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Dopamine D-2 Receptor Mechanisms In The Nucleus Accumbens Involved In Signal Transmission From The Hippocampus To The Mesencephalic Locomotor Region

Charles Renkin Yang

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DOPAMINE D-2 RECEPTOR MECHANISMS IN THE NUCLEUS ACCUMBENS INVOLVED IN SIGNAL TRANSMISSION FROM THE HIPPOCAMPUS TO THE MESENCEPHALIC LOCOMOTOR REGION.

by

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of the requirements for the degree of
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ABSTRACT

The purpose of this study was to investigate, using electrophysiological and behavioural techniques, a mesolimbic dopaminergic mechanism in the accumbens that may regulate the hippocampal output signal transmission to the subpallidal area, and the pedunculopontine nucleus (PPN), an integral part of the mesencephalic locomotor region (MLR).

Electrical stimulation of the hippocampus activated accumbens neurones in urethane-anaesthetized rats. This excitation was attenuated by iontophoretic application of dopamine and by conditioning stimulation (10Hz) of the VTA. This attenuating effect was blocked by iontophoretic application of trifluoperazine or intraperitoneal injection of haloperidol (both dopamine antagonists), or by 6-hydroxydopamine lesion of the mesolimbic dopamine neurones.

The excitability of the axonal terminals of the hippocampal-accumbens neurones, was enhanced significantly by conditioning VTA stimulation, iontophoretic application of dopamine, its D-2 agonist (LY171555) and potassium, but not by a dopamine D-1 agonist (SKF38393). This enhancement persisted after ibotenic acid lesion of the accumbens. Furthermore, the enhanced terminal excitability produced by conditioning VTA stimulation was attenuated by iontophoretic application of a D-2 antagonist, sulpiride, but not by a D-1 antagonist, SCH23390.

Electrical stimulation of the hippocampus produced inhibitory responses in neurones recorded in the ventral pallidal and subpallidal areas. Some of these subpallidal neurones were also activated antidromically by stimulation of the PPN. The inhibitory responses were attenuated by microinjection of a glutamate antagonist, or by the dopamine D-2 agonist into the accumbens.

In unanaesthetized rat, locomotor responses elicited by unilateral microinjection of N-methyl-D-aspartic acid, an excitatory amino acid, into the hippocampus were reduced in a dose-dependent manner by a D-2 agonist, injected into the medial accumbens. This hippocampal-initiated hyperkinetic response was also reduced by injecting nipecotic acid, a GABA uptake inhibitor, or procaine into the subpallidal area. Injection of procaine into the PPN also reduced significantly this hyperkinetic response.

These results suggest that excitatory signal transmission from the hippocampus to the accumbens was modulated presynaptically by a dopamine D-2 receptor mechanism. The hippocampal output signals, relayed via the accumbens, reached the subpallidal sites and descended to the PPN. This hippocampal-accumbens-subpallidal-PPN connection may enable hippocampal(limbic) signals to gain access to the MLR and elicit locomotor behaviours associated with biological adaptation.

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LIST OF ABBREVIATIONS

DA	Dopamine
GABA	Gamma-amino butyric acid
GDEE	Glutamic acid diethyl ester
HIPP-ACC	Hippocampal-accumbens
MD	Medio-dorsal nucleus of thalamus
MLR	Mesencephalic locomotor region
NAC	Nucleus accumbens
NMDA	N-methyl-D-aspartic acid
NPA	Nipecotic acid
6-OHDA	6-Hydroxydopamine
PPN	Pedunculopontine nucleus
SMC	Supplementary motor cortex
SP	Subpallidal areas
STM	Subthalamic nucleus
VA/VL	Ventro-anterior and ventro-lateral nucleus of the thalamus
VP	Ventral Pallidum
VTA	Ventral tegmental area
ZI	Zona incerta

INTRODUCTION

The nucleus accumbens of the ventral striatum, which is ventro-medial to the caudate nucleus, was neglected for some years prior to two major research developments. Firstly, it has been shown with the histofluorescence technique that the nucleus accumbens is one of the major target sites of midbrain dopaminergic neurones (Dahlstrom and Fuxe, 1964). Secondly, advances in neuroanatomical tracing techniques made it possible to demonstrate the afferent and efferent connections of the nucleus accumbens (Nauta et al.,1978). From these investigations, the accumbens was shown to be closely linked to many limbic structures and, in turn, to project to motor effector sites. For these reasons, the accumbens is now considered an 'interface' between the limbic and the motor systems (Mogenson et al.,1981; Mogenson, 1984).

An understanding of the anatomical connections of the accumbens has led to specufations regarding their functional significance. Some of the major afferents to the accumbens are from limbic structures including the hippocampus, amygdala, olfactory tubercle and the cingulate gyrus (Powell and Lehman,1976). In turn, the output neurones of the accumbens reach an area ventral to the globus pallidus (designated the ventral pallidum)(Nauta et al.,1978; Heimer and Wilson, 1975) and a more caudal region which includes

the substantia innominata and the lateral hypothalamus (designated subpallidal region)(Mogenson et al.,1983). More recently, a pathway linking the subpallidal region to the pedunculopontine nucleus of the brainstem has been identified (Swanson et al.,1984). The pedunculopontine nucleus is part of the mesencephalic locomotor region which contains the neural mechanisms for initiating rhythmic limb movements (Grillner and Shik, 1973; Garcia-Rill,1986). It was suggested that this subpallidal-pedunculopontine connection provides a final link which enables limbic inputs to the accumbens to be integrated into locomotor movement (Mogenson,1984).

The hippocampus is the source of the major limbic inputs to the nucleus accumbens (Kelley and Domesick, 1983; Swanson and Cowan, 1977). Electrical activity of the hippocampus is related closely with some types of voluntary movements. Moreover, the firing pattern of single hippocampal neurones correlates well with particular spatial orientation of animals (see Historical Review). Thus, a behavioural response involving locomotor activity may be initiated by neuronal activities of the hippocampus which provide the appropriate spatial information to the motor system. Accordingly, the output signals of the hippocampus may be relayed via the accumbens, to subpallidal sites and, subsequently, activate the mesencephalic locomotor region for movement.

The multiple converging limbic inputs to the accumbens and the restricted output from this nucleus which funnel the limbic signals to the ventral and subpallidal regions impose a high input to output ratio of the information transferred on the accumbens. To regulate this signal transmission through the accumbens, the mesolimbic dopaminergic neurones from the VTA of the midbrain projecting to the accumbens may exert a 'gating' effect (Stevens, 1979). However, the mechanisms by which dopamine exerts its 'gating' influence on limbic inputs to the accumbens are largely unknown.

In this study electrophysiological and behavioural techniques were used to investigate the functional linkages between hippocampus, nucleus accumbens, ventral and subpallidal regions and the pedunculopontine nucleus. The interaction of the mesolimbic dopaminergic system with limbic inputs in the accumbens, and the possible mechanisms by which dopamine influences these inputs to regulate signal transmission, were also studied. Extracellular single unit recordings were made from the nucleus accumbens, as well as from the subpallidal areas of anaesthetized rats. The effects of hippocampal stimulation on the firing pattern of accumbens neurones and the subsequent interaction with the mesolimbic dopaminergic neurones by stimulating the VTA or iontophoretic application of dopamine, were investigated. In order to study a possible presynaptic 'gating' action of

dopamine on the axonal terminal of hippocampal-accumbens neurones a terminal excitability test, modified from that originally developed by Wall(1958), was used. The accumbens output neurones which receive hippocampal signals were also identified by antidromic stimulation of the ventral pallidal and subpallidal regions. Further investigation of the transmission of hippocampal signals to the pedunculopontine nucleus were studied when recordings were made in the subpallidal sites. The same subpallidal neurones which responded to hippocampal stimulation were antidromically activated by pedunculopontine nucleus stimulation. Selective agonists for dopamine receptor subtypes were injected into the accumbens in order to test the hypothesis that dopamine may exert a 'gating' influence in the accumbens on the signal throughput from the hippocampus to the mesencephalic locomotor region.

Quantitative observation of locomotor activity of unanaesthetized animals in an open-field test was used as a simple behavioural assay. The locomotor responses was initiated by injecting an excitatory amino acid into the hippocampus. The dopaminergic 'gating' of hippocampal-induced kinetic responses was studied by injecting a dopamine agonist into the accumbens. The transmission of hippocampal signals via the subpallidal and pedunculopontine sites to elicit locomotor movement was investigated by injecting a GABA uptake inhibitor, or procaine, into the

subpallidal site, while procaine was also injected into the pedunculopontine nucleus.

Observations from these experiments are consistent with the hypothesis that the accumbens provides a relay site for hippocampal signals to the subpallidal area. Hippocampal signal transmission to the MLR is regulated by a dopaminergic mechanism in the accumbens, involving presynaptic inhibition. Based on these observations, an integrated model dealing with signal transmission from the hippocampus to the MLR via the hippocampus-accumbens-ventral and subpallidal areas-pedunculopontine nucleus is proposed.

HISTORICAL REVIEW

This thesis is concerned with the regulation and transmission of hippocampal signals to motor effector sites of the basal forebrain and brainstem to elicit locomotor activity. A review of each component closely associated with these neurophysiological processes is presented in the following sections.

1. Nucleus Accumbens

The nucleus accumbens occupies the ventromedial fundus of the rostral mammalian neostriatum. This nucleus is demarcated medially from the adjacent septal nucleus by the ascending and descending fibres of the septum. The rostral border of the accumbens is the anterior olfactory nucleus and the ventral accumbens is joined with the olfactory tubercle by cell bridges, from the interposing 'olfactory radiations' (Johnston , 1913; 1923; Heimer et al.,1982; Switzer et al.,1982). Caudally, the accumbens gradually merges with the bed nucleus of stria terminalis at the level of the anterior commissure. The accumbens is considered an integral part of the dorsal striatum because of their close similarities with respect to the development, cyto-architecture and histochemistry (Heimer and Wilson, 1975; Heimer 1978; Swanson and Cowan, 1975). However, because of the unique limbic inputs to the ventral striatal region, as compared to the dorsal striatum, the accumbens has also been referred as the 'limbic striatum'(Nauta and Domesick, 1977).

1.1 Major Afferent Connections

Limbic cortical inputs to the accumbens mainly terminate in the lateral portion of the nucleus. They originate from the inferior temporal cortex (in monkey: Whitlock and Nauta, 1956), the perirhinal cortex (in gerbil: Newman and Winans, 1980) and the prefrontal cortex (in rats: Phillipson and Griffiths, 1985). The hippocampus provides one of the major afferent inputs from limbic structures. Neurones of the ventral subiculum of the hippocampus project via the fimbria-fornix to the medial accumbens, avoiding the dorsal striatum entirely (Kelley and Domesick, 1983; Nauta, 1956; 1958; Raisman et al.,1966; Swanson and Cowan, 1977; Zaczek et al.,1979). In rats and cats this hippocampal-accumbens projection distributes topographically. Thus, ventral subicular neurones of the hippocampus project mainly to the medial sector of the accumbens. Successively more dorsal regions of the subiculum project to successively more ventrolateral regions of the rostral accumbens (Groenewegen et al.,1982; Kelley and Domesick, 1983; Phillipson and Griffiths, 1985). There is evidence that hippocampal-accumbens projections are glutamatergic (Walaas,1979; Fonnum and Walaas, 1980) which is consistent with the finding that subicular or fimbria stimulation elicites excitatory responses in neurones of the accumbens (Defrance and Yoshihara, 1975; Lopes da Silva et al.,1984).

Another major limbic input is from the basal lateral nucleus of the amygdala which projects to the anteromedial accumbens as well as to the entire dorsal striatum except an anterolateral quadrant (Krettek and Price, 1978; Kelley et al.,1982; Royce, 1978; Phillipson and Griffiths, 1985; Veening et al.,1980). Additional inputs to the accumbens come from the thalamus. The thalamic nuclei which project mainly to the anterolateral accumbens include the para-taenial, paraventricular, reuniens, medial parafasicular, rhomboid and central medial nuclei (Kelley and Stinus, 1984; Newman and Winans, 1980; Phillipson and Griffiths, 1985).

Histofluoresence studies of monoaminergic neurones have demonstrated a massive innervation of the accumbens by mesolimbic dopaminergic fibres which originate from the ventral tegmental area (VTA)(Dahlstrom and Fuxe, 1964). Serotoninergic neurones from the dorsal raphe nucleus also project to the accumbens (Miller at al.,1978; Steinbusch, 1981). In rabbits, noradrenergic fibres project from the locus coeruleus to the caudal accumbens. However, the concentration of noradrenaline is at least five times lower than the mean concentration of dopamine in the accumbens (DeFrance et al.,1983). Hence, the dopaminergic neurones appear to be the primary source of the monoaminergic innervation of the accumbens. A more detailed account of this mesolimbic dopaminergic innervation in the accumbens will be presented in section 3 of the Historical Review.

1.2 Major Efferent Connections

The output neurones of the accumbens, unlike those from the dorsal striatum, do not project to the internal segment of the globus pallidus (entopeduncular nucleus in non-primates), but instead, project to the ventral extension of the globus pallidus now designated the 'ventral pallidum' (Heimer and Wilson, 1975; Nauta et al.,1978) which includes part of the lateral preoptic area. The accumbens efferents also project caudally along the medial forebrain bundle, to a sublenticular subpallidal region which includes the substantia innominata and the lateral hypothalamus (Mogenson et al.,1983).

Additional accumbens efferents also project to the substantia nigra pars compacta, the source of the nigro-striatal dopaminergic neurones, as well as the dorsal layer of the pars reticulata division of the nigra (Nauta et al.,1978; Scarnati et al.,1983) and the adjacent VTA (Conrad and Pfaff, 1976; Phillipson, 1978). A substantial portion of these accumbens efferents to the substantia nigra, as well as those projecting to the ventral pallidum, are GABAergic (Nagy et al.,1977; Ribak et al.,1979; Walaas and Fonnum, 1979b; 1980). Electrical stimulation of the accumbens inhibited nigral cell firing (Scarnati et al.,1983) while such stimulation also inhibited pallidal cell firing (Mogenson et al.,1983) and iontophoretic application of

picrotoxin reversed the inhibition by GABA of pallidal neuronal firing (Jones and Mogenson, 1981). These electrophysiological findings support the suggestion that the accumbens-pallidal pathway is GABAergic (Nagy et al.,1978; Ribak et al., 1979).

More caudally at the brainstem level, accumbens efferents were shown to project to the pedunculopontine nucleus and to the central gray in rats and cats (Groenewegen et al.,1985; Moon-Edley and Graybiel, 1984; Nauta et al.,1978).

1.3 Putative Transmitters and Their Functional Interactions in The Nucleus Accumbens

Recent immunohistochemical findings have shown that a complex network of neurotransmitter systems is present in the accumbens. The dense dopaminergic innervation of the nucleus accumbens has directed attentation to the possible functions of dopamine in the accumbens. Depletion of dopamine in the accumbens by the catecholamine neurotoxin 6-hydroxydopamine results in a decrease in spontaneous, as well as in amphetamine induced motor activity in rats (Kelley et al.,1975). In addition, these lesioned rats showed less exploration of novel objects and had difficulty in suppressing on-going behaviour (temporal and spatial perseveration). They also exhibit inflexibility of behavioural switching and an enhanced latency to initiate motor responses (Taghouti et al., 1985). In sharp contrast

to the results which have been obtained with 6-OHDA lesion (Kelley et al.,1975), bilateral electrolytic lesions of the accumbens produced an overall increase in spontaneous locomotor activity (Lorens et al.,1970) but the amphetamine-induced hyperkinetic response was attenuated (Wirtshafter et al.,1978). This suggest that the amphetamine-induced hyperkinetic activity does not only involve the release of dopamine in the accumbens, other brain sites may also be mediating this hyperkinetic response.

Administration of dopamine or its agonists to the accumbens of unrestrained cats, rats and monkeys, on the other hand, produced an organized motor responses. These include increased vigilance, searching, pacing and submissive posture. These responses were prevented by administration of the dopamine receptor antagonist, haloperidol (Costall and Naylor, 1975; Jones and Mogenson, 1980; Jones et al.,1981; Pijnenberg et al.,1975,1976). It has been suggested that activation of the accumbens dopaminergic system elicits a heightened search for "meaning" in the environment (Iversen and Koob, 1977).

Other transmitter systems appear to regulate dopamine release in the accumbens, thereby influencing subsequent dopamine-mediated motor responses. Acetylcholine (De Belleroche and Gardiner, 1982d) and glutamate (Roberts and Anderson, 1979; Marien et al.,1983) have been shown to release dopamine from the accumbens <u>in vitro</u>. Muscarinic

agonists for acetylcholine receptors influence dopaminergic neurones to produce a hypermotor response that can be abolished by a 6-hydroxydopamine lesion of the dopaminergic afferents in the accumbens (De Belleroche et al.,1979; 1982a;1982b). Similarly, the injection of excitatory amino-acid analogues (glutamate receptor agonists) into the accumbens produces hypermotility in rats, and this action is blocked by dopamine antagonists. Glutamate may release dopamine which acts on the post-synaptic dopamine receptor, or may directly stimulate the glutamate receptors in the accumbens to produce the hyperkinetic response (Arnt, 1981; Donzanti and Uretsky, 1983;1984; Marien et al.,1983). On the other hand, dopamine, via its D-2 receptor, also inhibits the presynaptic release of glutamate (Mitchell and Doggett, 1980; Rowland and Roberts, 1980) and acetylcholine (De Belleroche et al.,1982c; Hertting et al.,1980; Lehamann and Langer, 1983; Stoof and Kebabian, 1982).

Activation of several neuropeptidergic systems in the accumbens also initiates locomotor responses in rats. Locomotor activity produced by direct stimulation of the opiate receptors in the accumbens is independent of the mesolimbic dopaminergic system since 6-hydroxydopamine lesions in the accumbens are ineffective in blocking the enkaphalin-induced hyperactivity (Havemann and Kuschinsky, 1985; Kalivas et al.,1983; Pert and Sivit, 1977).

Neurotensin is found in mesolimbic neurones which project from the VTA to the medial accumbens (Kalivas and Miller, 1984). Injection of neurotensin into the medial accumbens blocks locomotion and rearing initiated by coinjection of dopamine, or of opiate peptide, into the same site. It was suggested that neurotensin in the accumbens antagonizes general behavioural hyperactivity, regardless of which neurochemical initiates it (Kalivas et al.,1984).

Of the several known neuropeptide systems in the accumbens, the cellular effects of only cholecystokinin (CCK) has been studied in detail. CCK was found to co-localize with dopamine in a sub-population of VTA neurones (Hokfelt et al.,1980;1983; Skirbol et al.,1981). Firing of accumbens neurones is enhanced by CCK and this exitatory effect is reversed by dopamine, suggesting that dopamine and CCK jointly modulate activity of medial accumbens neurones (Skirboll et al.,1981; White and Wang, 1984). On the other hand, CCK has also been found to reduce dopamine release from the accumbens <u>in vivo</u> and this peptide antagonizes dopamine-dependent behaviours thought to be mediated by the accumbens (Van Ree et al.,1983; Voigt and Wang, 1985). These findings indicate that multiple transmitter systems in the accumbens regulate the post-synaptic dopamine receptors to engage the accumbens output in locomotor responses. This is consistent with the view that the accumbens may be involved in translating limbic antecedents into action (Mogenson,1984).

2. Hippocampus

The hippocampus provides one of the most prominent limbic inputs to the accumbens. The known functions of this limbic structure in memory and spatial orientation suggest that it is an important source of signals to the accumbens which relays them to motor effector sites to initiate actions.

2.1 Anatomical Divisions

The hippocampus belongs to a part of the cerebral cortex which forms a horn-shaped body along the curvature of the lateral ventricles. This cortical region is subdivided into the hippocampus proper (cornus Ammonis,CA; or Ammon's horn), the fascia dentata (dentate gyrus) and the subicular complex (including the prosubiculum, subiculum, presubiculum and parasubiculum) which is contiguous to the entorhinal cortex (Cajal,1911; Lorente de No, 1934). The cell layers of the hippocampus proper are made up of lamellae with each being an individual anatomical unit consisting of four fields: CA1,CA2,CA3 and CA4.. The main flow of information within each lamella is transmitted by excitatory glutamate/aspartate synapses in the direction of dentate area (CA4), CA3 and thence to CA1 in a topographical manner (see Chronister and White,1975; Lopes da Silva and Arnold, 1978). In addition, a set of GABAergic inhibitory interneurones, the basket cells of Cajal (Cajal,1911) which

distribute in each lamella, appears to control the excitatory flow of the tri-synaptic circuit by recurrent inhibition (Schwartzkroin and Knowles,1983.)

2.2 Major Afferent Connections.

Two major afferent inputs to the hippocampus have been extensively studied. First, an excitatory glutamatergic perforant path from the entorhinal cortex, transverse the subiculum, presubiculum, and terminates in the granule cell layers of dentate area and the CA3 field (Nadler et al.,1976; 1978; Storm-Mathisen, 1977; White et al.,1977). Since the entorhinal cortex receives cortical inputs of multiple modalities (Gross et al.,1967; 1969; Jones and Powell, 1970; Van Hoesen and Pandya, 1975; Van Hoesen et al.,1972), it was postulated that the perforant path conveys these cortical inputs to the hippocampus (Lopes da Silva and Arnold, 1978).

The second major input is the diffuse cholinergic projections from the medial septum to the hilus of the dentate area and CA3 field (Chandler and Crutcher,1983; Crutcher et al.,1981; Hjorth-Simonsen,1972; Lynch et al.,1978; Kuhar,1975; Pasquier and Reinoss-Suarez, 1977). The medial septum appears to be a critical source of cell discharges which impose a movement-related theta-rhythm in hippocampal neurones (Green and Arduini, 1954; Green et al.,1960; Vanderwolf and Leung, 1983; Bland, 1986).

2.3 Major Efferent Connections.

The neural projection from the hippocampus to the ventral striatum is of particular interest in this study in view of the nucleus accumbens being a limbic-motor interface which receives limbic afferents and which in turn, projecting to motor effector sites (Mogenson et al.,1980). Recent autoradiographic studies employing axonal tracing studies (Groenewegen et al.,1980; Kelley and Domesick, 1982; Swanson and Cowan,- 1975;1977) have confirmed earlier evidence for a direct hippocampal-accumbens connection through the precommissural fornix in different species (Heimer and Wilson,, 1975; Raisman et al.,1976; Newman and Winans, 1980).

This hippocampal-accumbens pathway appears to be glutamatergic, and stimulation of the fimbria or the ventral subiculum excites accumbens neurones (DeFrance and Yoshihara, 1975; Lopes da Silva et al.,1984; Walaas and Fonnum, 1979a). Destruction of the subicular fibres also leads to a 50% reduction in the high affinity uptake of glutamate together with a pronounced reduction of endogenous concentration of glutamate in the nucleus accumbens (Walaas and Fonnum, 1979a). The pyramidal cells of the ventral subiculum are also the origin of many other hippocampal efferents besides those projecting to the accumbens. Thus, transection of the descending fornix, the axonal fibres of these hippocampal efferents, also reduces the high affinity

glutamate uptake in the bed nucleus of stria terminalis and mammillary body. Nevertheless, no change in the endogenous level of aspartate, glutamine or other amino acids was observed (Fonnum et al.,1979; Walaas and Fonnum, 1979a).

Other extra-hippocampal efferents travel along the alveus and fimbria, and divide at the level of the anterior commissure to form pre- and post-commissural fornix systems which project to areas of the forebrain and the midbrain as follows:

i) Axons arising from the CA1 and CA3 project via the precommissural fornix to the lateral septum (Swanson and Cowan, 1977);

ii) A caudally-directed projection from the CA3 region terminates in the entorhinal area (Votaw,1960; Hjorth-Simonsen, 1971);

iii) The subicular complex receives innervation from CA1 and CA3 neurones and projects topographically via the fimbria-fornix system to both pre- and post-commissural systems. Dorsal subiculum projects predominatly to the mammillary complex and the thalamus via the post-commissural fornix system (Meibach and Siegal,1977; Chronister et al.,1975). Ventral subiculum is responsible for most of the hippocampal output to the rostral hypothalamus by way of the medial cortico-hypothalamic tract. Via the pre-commissural fornix,

ventral subiculum sends its fibres, in additional to the nucleus accumbens of the ventral striatum, to the anterior olfactory nuclei, the taenia tecta and the bed nucleus of stria terminalis as well as the lateral septum (Swanson and Cowan,1977).

2.4 Functions of the Hippocampus

It has been suggested that the hippocampus contributes to the 'mapping' of the external spatial environment, and serves as a 'sorter' or 'cross-correlator' for assessing the significance of incoming stimuli (O'Keefe and Nadel,1978; Teyler and DiScenna,1984). Hippocampal electrical activity is also associated with certain types of voluntary movement (Vanderwolf, 1969,1971). Additional evidence suggests that the hippocampus may play a part in regulating the hypothalamic-pituitary-adrenal axis (McEwen et al.,1968; 1970; van Hartesveldt, 1975).

The involvement of the hippocampus in spatial orientation was first shown in lesion studies demonstrating deficits in the estimation of space and time not entirely due to a lack of attention for new stimuli (O'Keefe et al.,1975; Olton, 1976; Plunkett et al.,1973). In open fields to which the lesioned animals were not accustomed, these animals exhibited enhanced motor activity. However, these animals did not systematically inspect the whole environment as do normal rats, nor did they decrease their locomotor

activity over time (habituate) as do the normal animals. This led to the suggestion that the lesioned animals "have not incorporated information about the new environment into a spatial mapping system in their hippocampus" (O'Keefe and Nadel, 1978).

Additional evidence indicating the hippocampus is involved in spatial orientation came from the experiments using an eight-arm radial maze. When all the arms of this maze are baited with food at each end, food-deprived rats learned the strategy, using the hippocampus, to visit each arm once and obtained their food as reward. It appears that this 'strategy' was employed because it would not be adaptive to return continuously to the same arm after all the food available had been consumed. Bilateral hippocampal lesions, or disconnections of major extrinsic connections, produced severe deficits in this task so that the animals performed in the maze at chance levels (from a mean pre-lesion score of 7.5 on the first 8 choices of arms in 20 trials)(Olton et al., 1982).

More direct evidence for the hippocampus as one of the key sites for processing information regarding the spatial orientation of the animal came from single-unit recording experiments obtained from freely-moving rats (Ranck, 1973) on a T-shaped or an eight-armed radial maze (Olton et al.,1978a; O'Keefe, 1976; O'Keefe and Conway, 1978). Single hippocampal units changed their firing rate when the rat was

at a specific location of the arm in the maze. Removal of some of the extra-maze cues from the environment either reduced, or increased, the firing rate of these cells in the place field irrespective of its behaviour in that location. Thus, spatial factors appear to contribute to the firing pattern of these hippocampal neurones. From such recording experiments, it was inferred that hippocampal unit activity may signal the animal's position in an environment by indicating a "mismatch" between the sensory inputs arriving in the hippocampus from a part of the environment and those which would be expected on the basis of the animal's memory representation from previous experiences of that place registered in the hippocampus. It is conceivable that following intra-hippocampal processing of these signals, the output of these units to extra-hippocampal sites provides initiation signals to the motor system for expressing the hippocampal-mediated adaptive behaviours, such as exploration, searching or location of food, water or mates. Judging from the anatomical standpoint, the nucleus accumbens appears to be located strategically to receive such hippocampal output and subsequently, relay it to motor effector sites of the basal forebrain (Mogenson, 1984).

3. Central Dopaminergic Systems

The mesolimbic dopaminergic system which originates from the VTA and projects to the nucleus accumbens is

most relevant to the studies conducted and so it will be emphasized in this review. Other divisions of the central dopamine system will be considered only briefly. In addition, since the dopaminergic actions were studied extensively in the nigrostriatal pathway, most of these findings are thus taken as the basis for studying the basic actions of dopamine in the accumbens.

3.1 Divisions of Central Dopaminergic Systems

i) Nigrostriatal pathway: dopaminergic neurones from the substantia nigra pars compacta region (A9) project to the caudate-putamen complex of the neostriatum.

ii) Mesolimbic/mesocorticalpathways: dopaminergic neurones from the ventral tegmental area (VTA)(A10) project upon the olfactory tubercle and the adjacent structures including isocortex (medial frontal, anterior cingulate, entorhinal, perirhinal cortices), allocortex (olfactory bulb, anterior olfactory nucleus, olfactory tubercles, piriform cortex, septal area, nucleus accumbens, amygdaloid complex)(see Dahlstrom and Fuxe, 1964).

iii) Tubero-hypophyseal system: dopaminergic neurones from the arcuate and periventricular hypothalamic nuclei project to the neurointermediate lobe of the pituitary as well as to the median eminence.

iv) Incerto-hypothalamic pathways which project from the zona incerta, posterior hypothalamus to dorsal hypothalamic area and septum;

v) Periventricular pathway which project from the medullary area of dorsal motor vagus, nucleus tractus solitarius, periaqueductal and periventricular gray to tectum (see Moore and Bloom, 1979).

3.2 Types and Locations of Dopamine Receptors

Following the discovery of dopamine in the mammalian central nervous system (Carlsson et al, 1958; Montagu, 1957; Weil-Malherbe and Bone, 1957), the existence of receptor(s) specific for dopamine was postulated to account for the biochemical, behavioural and physiological effects of dopamine on the CNS (Anden et al, 1966; Ernst, 1969; Ungerstedt, 1971). Several investigators proposed as few as one, or as many as four distinct receptors for dopamine (see Stoof and Kebabian, 1984). Fortunately, there is a general consensus now that two major categories of dopamine receptors exist in the mammalian CNS, designated D-1 and D-2 receptors.

D-1 receptors are coupled to adenylate cyclase and activation of this receptor increases the formation of cAMP. Via a cascade reaction, cAMP activates various kinases in the neurone, resulting in membrane protein phosphorylation which regulates ionic fluxes in and out of the neurone (Greengard, 1978). Recently, a dopamine and cAMP-regulated

phosphoprotein with an apparent molecular weight of 32,000 dalton (DARPP-32) has been shown to be associated specifically with the D-1 receptor sites (Ouimet et al., 1984; Walaas and Greengard, 1984). Thus, DARPP-32 has become a physiological marker for identifying dopamine D-1 receptors which have been shown to be richenot only in the corpus striatum, but also in the nucleus accumbens, amygdala, bed nucleus of stria terminalis and the olfactory tubercles.

D-2 receptors, on the other hand, either are not associated with adenylate cyclase or stimulation of this receptor results in an inhibition of adenylate cyclase and consequently, a reduction in cAMP formation (Stoof and Kebabian, 1984; Weiss et al.,1985; Onali et al.,1985). Furthermore, both post-synapaic D-1 and D-2 receptors can be present on the same neurone since dopamine can stimulate, as well as inhibit, the formation of cAMP. Dopamine, or a selective D-1 agonist, SKF38393, stimulates cAMP formation in striatal slices, in accordance with its ability to stimulate the adenylate cyclase activity via D-1 receptor activation. A selective D-2 raceptor blocker, sulpiride, potentiates this D-1 receptor-stimulated cAMP formation with no appreciable changes in the molar potency of dopamine (Stoof and Kebabian, 1982). Since a D-2 agonist reduces this generation of cAMP induced by D-1 receptor activation in a non-competitive manner, it was suggested that in the

neostriatum there is a D-2 receptor which inhibits cAMP formation brought about by D-1 receptor stimulation.

In addition to its location on post-synaptic membrane, D-2 type dopamine receptors are also located on both the axonal terminals, and on the somadendritic region of the dopaminergic neurones. They are called autoreceptors since these receptors auto-regulate dopamine release and biosynthesis. Thus, release of dopamine from striatal slices by high extracellular concentration of potassium is inhibited by dopamine and D-2 receptor agonists, and this inhibition can be reversed by D-2 antagonists (Kamal et al.,1981; Starke et al.,1978; 1983; Stoof et al.,1980). The action of dopamine on the autoreceptors located on the striatal dopaminergic axonal terminal region has also been determined electrophysiologically by using the terminal excitability test. Infusion of dopaminergic agents, e.g. apomorphine or amphetamine, into the striatum decreased the probability of eliciting antidromic responses in the substantia nigra pars compacta dopaminergic cell body region to caudate stimulation (Mereu et al.,1985; Tepper et al.,1984). This decrease in the terminal excitability of dopaminergic neurones was reversed by dopamine antagonists. Since intra-terminal recording in mammalian CNS is technically impossible at present, the action of dopamine in decreasing the terminal excitability of dopaminergic neurones was inferred to be associated with a dopamine

autoreceptor-mediated hyperpolarization of their striatal terminals and thus to produce an auto-inhibition of dopamine release (Mereu et al.,1985; Tepper et al.,1984). Furthermore, biosynthesis of dopamine in striatal synaptosomes or slices was also inhibited by dopamine or its D-2 agonist (Bitran and Bustos, 1982; Saller and Salama, 1984). Hence, activation of D-2 autoreceptors on dopaminergic axonal terminals attenuates dopamine release and synthesis in response to the presence of dopamine in the synaptic cleft---- a process of autoregulation.

On the soma-dendritic region of the A10 dopaminergic neurones in the VTA, there is also a D-2 type autoreceptor. Iontophoretic application of D-2 agonists on these VTA dopaminergic neurones suppresses their spontaneous firing (White and Wang, 1984).

Another population of post-synaptic dopamine receptors is located on the axonal terminals of non-dopaminergic neurones. In the caudate nucleus, these receptors appear to be D-2 type and are located on the glutamatergic cortico-striatal terminals, and the nigrostriatal dopaminergic neurones regulate the release of glutamate from these excitatory afferent terminals (Brown and Arbuthnott, 1983; Godukhin et al.,1984; Mitchell and Doggett, 1980; Nieoullon et al.,1983a; Rowland and Roberts, 1980; Schwarcz et al.,1978; Theodorou et al.,1981).

In summary, it is now known that both D-1 and D-2 dopamine receptors are present in the striatum. Stimulation of D-1 receptors is coupled to adenylate cyclase activation and a synthesis of the intracellular messenger cAMP which, subsequently, mediates a variety of biochemical events including phosphorylation of a specific protein called DARPP-32. These phosphoproteins may represent some of the ion channel proteins which regulate ionic fluxes and consequently, the excitability of the neurones (Greengard, 1978). In contrast, stimulation of D-2 receptors inhibits adenylate cyclase as well as the D-1 receptor-induced cAMP formation in the striatum. Apart from their location on the postsynaptic membrane of striatal neurones, D-2 receptors are also present on the axonal terminals of non-dopaminergic striatal afferents, e.g. corticostriatal neuronal terminals postsynaptic to nigrostriatal dopaminergic neurones. Dopamine autoreceptors also exhibit D-2 receptor characteristics and are found to be located on the somadendritic regions of dopaminergic neurones as well as on their axonal terminal. Activation of these D-2 receptors inhibits dopamine synthesis and firing rate of these neurones.

3.3 Cellular Actions of Dopamine

Dopamine usually inhibits the firing of striatal neurones when applied iontophoretically to striatal neurones

(Connor, 1970; McLennan and York, 1967; White and Wang, 1985; Yim and Mogenson, 1982; York, 1967). However, in a few cases, a predominant increase of neuronal firing has also been reported (Bevan et al.,1975; Mintz et al.,1986; Norcross and Spehelmann, 1978). When recordings were made intracellularly from striatal neurones, iontophoretic application of dopamine produced a slow membrane depolarization of up to 15 mV, often with no change, or an increase in apparent membrane input resistance (i.e. decrease in conductance) as well as an overall suppression of spike generation (Bernardi et al., 1978;1982; Herrling and Huli, 1980; Mercuri et al.,,1985; Yim and Mogenson, 1986). In slice preparations of rat hippocampus dopamine causes a prolonged inhibition of spike generation from CA1 pyramidal neurones and is associated with hyperpolarization and an increase in conductance. The increase in conductance appears to be derived from an induction of a Ca^{++} -activated-K^{+} -conductance which results in an augmentation of the after-hyperpolarization (Bernardo and Prince, 1982a; 1982b; Haas and Konnerth, 1983; Stazione et al.,1984; Suppes et al.,1985). Thus, at post-synaptic sites dopamine produces different effects on hippocampal and striatal neurones.

3.4 Physiology and Pathophysiology of the Mesolimbic Dopaminergic System.

The A10 mesolimbic dopaminergic system has been implicated in mediating patterns of locomotor and

exploratory behaviours essential to the survival of an animal (Simon and Le Moal, 1984). Lesions of these dopaminergic neurones result in a disruption of the integrative functions of this A10 system responsible for modulating these behaviours (Stinus et al.,1978; Gaffoni and Le Moal, 1979) as mentioned in section 1.4. In contrast, self-administered electrical stimulation of these dopaminergic neurones has reinforcing properties since there is an increased likelihood of the animal returning to the lever that delivers the electrical pulses (Corbett and Wise, 1980; German and Bowden, 1974; Robertson and Mogenson, 1978). Hence, it has been postulated that the mesolimbic dopaminergic system provides the 'drive' for the integrative processes which modulate the organization of adaptive and productive patterns of behaviours necessary for survival (Mogenson et al.,1980).

3.4.1. Locomotor Responses in Adaptive Behaviour

Dopaminergic synapses in the nucleus accumbens are particularly important in locomotor activity. Direct injection of dopamine into the accumbens causes a strong stimulation of locomotor activity (Kelley et al.,1975; Pijnenburg et al.,1975). Intraperitoneal injection of amphetamine releases dopamine from the dopaminergic terminals and the enhanced locomotor activity following amphetamine injection is antagonized specifically by

injecting dopamine receptor blockers into the accumbens, but not into the caudate nucleus (Pijnenburg et al.,1975; Kelley et al.,1975). Stereotypic behaviour induced by d-amphetamine, on the other hand, appears to be antagonized by dopamine receptor blockers injected into the caudate, but not into the accumbens (Costall et al., 1975). These findings suggest that caudate dopaminergic synapses mediate stereotypic behaviour, while the accumbens dopaminergic synapses mediate ambulatory locomotor behaviour.

The mesolimbic dopaminergic system is also important in more complex adaptive behaviours such as feeding and drinking. The dopamine metabolite dihydroxyphenylacetic acid (DOPAC), one of the indicators of dopamine release, was observed to increase only in the terminal fields related to limbic functions, e.g. nucleus accumbens, posterior hypothalamus and amygdala, when fasted rats were allowed to eat (Heffner et al.,1980). This increase in dopamine release has been attributed to the motor act of food consumption rather than to the motivational consequence of fasting or stress developed from fasting (Mason, 1984). On the other hand, when dopamine is depleted in the accumbens by injecting 6-hydroxydopamine into the VTA or into the accumbens, the aphagia and adipsia is not as severe as that developed when similar depletion occurred in the caudate nucleus (Koob et al.,1978;1981). Thus, as far as feeding and

drinking are concerned, the dopaminergic innervation of the dorsal striatum appears to be more important than that to the nucleus accumbens or the olfactory tubercle (Mason, 1984).

3.4.2 Functional Correlates of Dopaminergic Unit Activity in Freely-Moving Animals

In freely moving cats and monkeys, single unit activity recorded from presumed dopaminergic neurones of the substantia nigra pars compacta showed bursting activity during the active waking state. However, these small changes of unit firing were not correlated with electromyographic (EMG) changes, nor did they appear to be associated with movement per se (DeLong et al., 1983; Schultz et al.,1983; Steinfels et al.,1983; Trulson,1985).

The spontaneous activity of the nigral dopaminergic neurones appears to depend on the behavioural state. Auditory stimulation presented as clicks to these cats, produced excitation-inhibition responses in the recorded dopaminergic neurones. This response disappeared as the cat progressed into slow-wave sleep and the response was totally absent during REM sleep but reappeared upon waking (Steinfel et al.,1983). This indicates that the responses of the dopaminergic neurones are strongly state-dependent. During an orientation response to a novel stimulus , e.g. opening of the cage door, the dopaminergic neurones of the cat fired in short bursts. As the cat fixated to the

stimulus, a long-lasting depression of the unit from further firing was observed. The absence of dramatic changes in the firing pattern of these dopaminergic neurones that parallel the activity of muscle groups rules out a role of the dopaminergic neurone in information transmission which could encode parameters of movement. Rather, these nigrostriatal dopaminergic neurones may play a tonic modulatory role in maintaining motor function especiallly when the animal changes its state from resting to active moving (Schultz et al.,1983).

3.4.3. Pathophysiology of Mesolimbic Dopaminergic System.

Dopamine receptors of the mesolimbic dopaminergic system have been associated with several debilitating psychiatric and neurological disorders including schizophrenia and Parkinson's disease. The most effective drugs in ameliorating schizophrenic symptoms also block or reduce functional activity of neuronal systems directly influenced by the central dopaminergic systems. This led to the suggestion that the neuropathology of the mesolimbic dopamine system is involved in schizophrenia because of its primary influence on limbic areas (Stevens, 1979). Increase in the level of dopamine in the nucleus accumbens of human post-mortem schizophrenic brains, or increase in the number of dopamine D-2 receptors in these brains have been reported (Bird et al.,1979; Cross et al.,1981; Lee and Seeman, 1980;

Owen et al.;1978). However, several complications have prevented the establishment of a clear causal relationship of dopamine with schizophrenia. For instance, the increase in the amount of dopamine in the brains of the schizophrenics are not replicated in all cases and the increase in dopamine receptors in the brains of these patients have been attributed largely to the effect of long-term treatment with neuroleptic drug (Reynolds et al.,1980; MacKay et al.,1980; Crow et al., 1979).

Problems in movement initiation and rigidity of limbs and resting tremor in Parkinsonian patients are related to the loss of dopamine-containing cells in the substantia nigra. Since there is an overlap of the A9 and A10 dopaminergic projections to the nucleus accumbens, dopamine was found to be depleted in the caudate nucleus as well as in the accumbens in Parkinsonian patients. It was suggested that akinesia in these patients might be the result of a combined deficiency of dopamine in the nucleus accumbens and caudate nucleus. Thus, dysfunction in the initiation of basic locomotor responses may be due to dopamine depletion in the accumbens whereas dysfunction in the initiation of finer movements involving cognitive processes may be due to dopamine depletion within the caudate nucleus(Price et al.,1978).

4. Ventral Pallidum and the Subpallidal Area.

From the nucleus accumbens, the output neurones project to the ventral portion of the globus pallidus, in the regions now designated ventral pallidum and the subpallidal areas. Judging from the course of their projections, there are striking similarities shared by the ventral striatal and the dorsal striatal pathways of the basal ganglia.

4.1 Neuroanatomical Linkages

A parallel was drawn recently between the dorsally connected neocortical-neostriatal-thalamocortical 'motor loop' with the connections in the ventral striatum and ventral pallidum (Heimer and Wilson, 1975; Alexander et al.,1986; Graybiel and Ragsdale, 1979; Kemp and Powell, 1971). Thus, neural fibres originating from the nucleus accumbens are shown to terminate in a rostral division of ventral globus pallidus underlying the anterior commissure (designated ventral pallidum, VP)(Heimer and Wilson, 1975; Heimer et al.,1982; Nauta et al.,1978; Conrad and Pfaff, 1976). These accumbens efferents also spread caudally to a subpallidal (SP) area, including the substantia innominata and the lateral hypothalamus (Mogenson et al.,1983; Groenewegen and Russchen, 1984). In turn, VP projects to the mediodorsal thalamus (MD)(Young et al.,1984; Vives and Mogenson, 1985) which projects to the prefrontal cortex and the anterior cingulate cortex (Beckstead, 1979; Krettek and

Price, 1977; Leonard, 1969; Siegel et al.,1977) and completes an allocortico-ventral striatal-ventral pallido-mediodorsal thalamocortical loop running in parallel with the classical 'motor loop' of the dorsal basal ganglia (Heimer and Wilson, 1975)(see Fig. 1).The dorsal striato-pallidal system plays a prominent role in initiating motor activities stemming from cognitive activities whereas the ventral striato-pallidal system may initiate movements in response to emotionally or motivationally significant stimuli (Heimer et al.,1982).

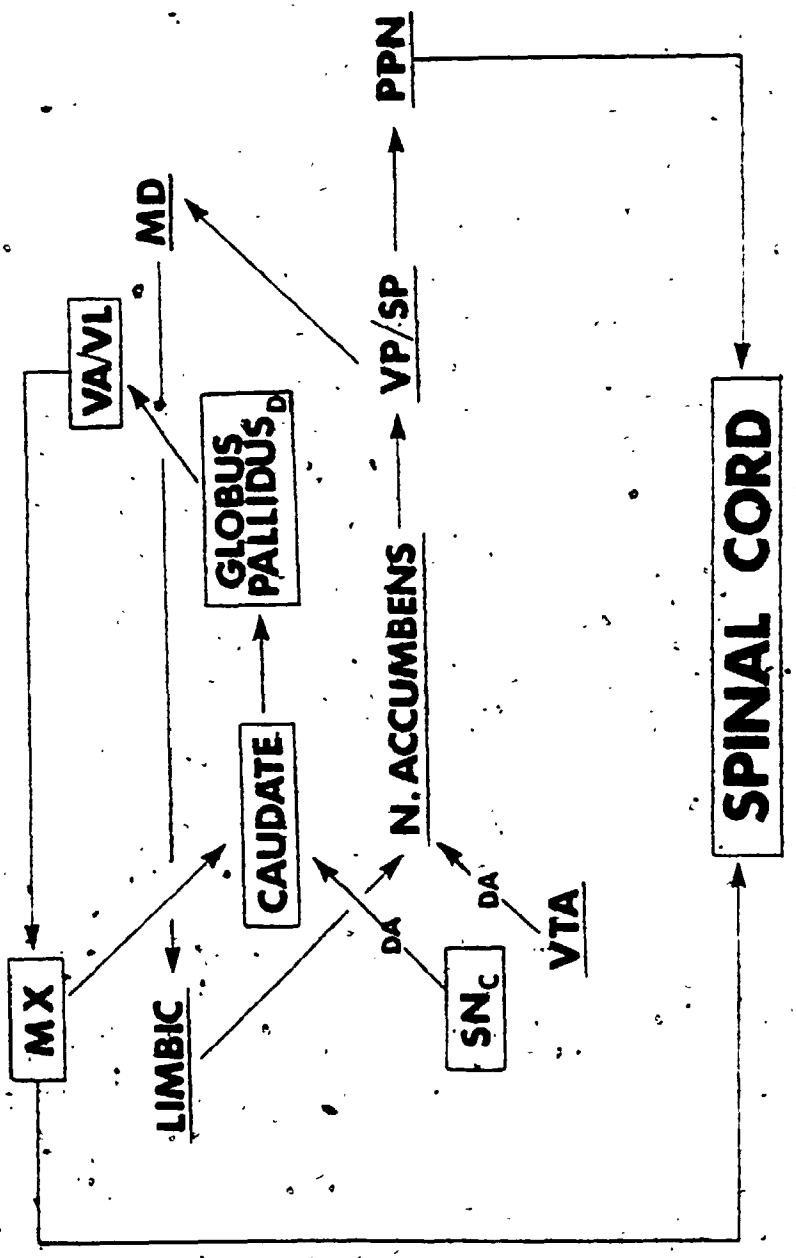
More recently, it was shown that the subpallidal area, receiving the more caudally-directed accumbens efferents, and descends to the nucleus pedunculopontinus including the adjacent central gray (Haber et al.,1985; Mogenson et al.,1983; Swanson et al.,1984) which have been considered as an integral part of the 'mesencephalic locomotor region' (MLR)(Garcia-Rill et al.,1981; Garcia-Rill, 1986; Grillner, 1985; Skinner and Garcia-Rill, 1984; see section on the MLR). It is this descending projection that has been postulated to have a role in conveying some of the limbic antecedents to the reticulospinal mechanisms for eliciting locomotor movements (Mogenson, 1984).

4.2 Neurotransmitter Systems in the Ventral and Subpallidal Areas.

The cytoarchitectural and histochemical features of neurones in the ventral and subpallidal areas share many

FIGURE 1

Block diagram illustrating parallel connections of the 'classical' and dorsally running cortico-striatal-pallidal-thalamo-cortical 'motor loop' with that of the ventrally connected limbic cortico-ventral striatal (nucleus accumbens)-ventral pallidal-thalamocortical route. Note that ventral pallidal/ subpallidal (VP/SP) signals may gain direct access to the spinal motor generating sites via the pedunculopontine nucleus (PPN). Inputs to both parts of the striatum are regulated by dopaminergic (DA) systems. The cortico-striatal pathway is regulated by the nigro-striatal dopaminergic neurones, while the allocortico-accumbens pathway is regulated by the mesolimbic dopaminergic neurones from the ventral tegmental area (VTA). Abbreviations: MX, somatomotor cortex; SNc, substantia nigra pars compacta; VA/VL, ventral anterior and ventral lateral nucleus of the thalamus.


PPN
MD
VA/VL
VP/SP
GLOBUS PALLIDUS D
N. ACCUMBENS
CAUDATE
SPINAL CORD
MX
LIMBIC
DA
DA
SNC
VTA

similarities with the neurones in the dorsal globus pallidus. A prominent GABAergic projection originates from the nucleus accumbens and terminates in the VP and SP. Thus, lesions of the nucleus accumbens drastically reduce the staining for glutamate decarboxylase, the enzyme responsible for the synthesis of GABA in VP and SP (Walaas and Fonnum, 1979). Likewise, stimulation of the accumbens inhibited the spontaneous discharge rate of VP/SP neurones (Mogenson et al.,1983; Dray and Oakley, 1977; Jones and Mogenson, 1980). Iontophoretic application of picrotoxin, a GABA antagonist, also blocked the inhibitory responses of the pallidal neurones to iontophoretic application of GABA (Jones and Mogenson, 1980). Some of these GABAergic neurones appear to regulate the ascending cholinergic neurones from the substantia innominata to the cortex (Fibiger, 1982; Lehamnn et al.,1980; McKinney et al.,1983; Saper, 1984).

Beside the GABAergic projection from the accumbens there are other striatopallidal projections. These accumbens output neurones are described as ribbon-like 'woolly fibres', immunoreactive to enkephalin and Substance P, which ensheath the dendrites of ventral pallidal neurones (Haber and Elde, 1981; Haber and Nauta, 1983; Groenowegen and Russchen, 1984). At least some of these peptidergic neurones synapse on the dense distribution of cholinergic neurones of the VP (Haber et al.,1985). However, it is uncertain whether

some of the neurones of the descending SP pathway are also cholinergic.

4.3 Functions of the Ventral Pallidum and Subpallidal Area.

The close association of the ventral pallidal and subpallidal areas with the limbic structures has prompted speculation that these areas participate in locomotor behaviour which involves motivational and goal-directed mechanisms, e.g. drinking. When Angiotensin II was injected as a dipsogenic agent into the rat cerebroventricles, the frequency of licking during drinking was reduced by injection of GABA into the vicinity of VP and SP. The latency to drink was also increased in the absence of oral motor deficits (Jones and Mogenson, 1982; Mogenson and Sztorc, 1982).

Increased ambulatory locomotor activity induced by injecting dopamine or its agonists into the nucleus accumbens was attenuated by injecting GABA agonists into the globus pallidus and into the vicinity of the VP (Jones and Mogenson, 1980b; Mogenson and Nielsen, 1983; Pycock and Horton, 1976; Slater et al.,1982). When the dopaminergic receptors are rendered 'supersensitive' following 6-hydroxydopamine lesions of the accumbens (Staunton et al.,1982), the hyperkinetic response produced by apomorphine stimulation of these 'supersensitive' receptors was blocked by electrical lesion of the SP area (Swerdlow et al.,1984). All these results suggest that a tonic inhibitory GABAergic

input from the accumbens to the VP and SP area may subserve dopamine-mediated locomotor response initiated by dopamine receptor stimulation in the accumbens. Hence, dopamine released from the VTA neurones in the accumbens may inhibit an inhibitory accumbens output to the VP and SP. A disinhibition action in the VP and SP produce an activation of locomotor response.

The activation of VP neurones by the dopaminergic input to the accumbens is better studied than the other inputs to the accumbens which may also activate locomotor responses via VP/SP. Recently, it was shown that the exploratory hyperkinetic locomotor activity elicited by the injection of carbachol into the dentate gyrus of the rat hippocampus, or by novel objects present in an open field were both attenuated by injecting GABA into the subpallidal region, as well as by a glutamate antagonist into the accumbens (Mogenson and Nielsen,1984a,1984b). This suggests that another afferent to the accumbens (from the hippocampus), in addition to the VTA dopaminergic input, may activate the accumbens-subpallidal neurones to elicit locomotor response.

5. Nucleus Tegmentipedunculopontinus (Pedunculopontine Nucleus)

From the subpallidal area output signals may elicit locomotor responses via its prominent projection to the motor cortex (McKinney et al.,1983; Saper, 1984). However, since decorticated animals with intact basal ganglia can

initiate normal goal-directed locomotor movements, it has been postulated that limbic pallidal efferents to brainstem motor effector sites may elicit locomotor activity (Mogenson, 1984). The pedunculopontine nucleus (PPN) of the brainstem has attracted a great deal of attention in motor physiology because of its reciprocal connections with the basal ganglia. More recently, chemical and electrical stimulation of PPN have been shown to induce rhythmic locomotor movements in decerebrate cats and rats (Garcia-Rill et al.,1983; Skinner and Garcia-Rill,1985; Mogenson and Wu, 1986). Thus, this nucleus is now also considered as an integral part of the MLR.

5.1. Pedunculopontine Nucleus and the Mesencephalic Lomotor Region.

The pedunculopontine nucleus (PPN) occupies an area in the brainstem that extends from the level of the occulomotor complex rostrally, to the parabrachial nuclei caudally. Anterograde and retrograde axonal tracing techniques have shown that the dorsal boundary of the PPN is formed rostrally by the deeper layers of the superior colliculus and caudally by the cuneiform nucleus and the inferior colliculus. The dorso-medial border of the PPN is not well-defined and a diffuse zone of this nucleus encompasses the adjacent lateral aspect of the periaqueductal gray and the medial longitudinal funiculus (Swanson et al.,1984).

When an area confined to the ventral and lateral part of the nucleus cuneiformis (at its boundary with the dorsal edge of brachium conjunctivum) was stimulated repetitively with low amplitude current pulses of 20-60 uA at 20-60 Hz in decerebrate (precollicular-post-mammillary transection) cats rhythmically coordinated treadmill walking was induced. This area of the brainstem was first defined as the 'mesencephalic locomotor region'. As the stimulation strength was increased, the speed and form of locomotion changed from a slow walk to a trot, or to a gallop which involves a continuous coordination of the four limbs and the spinal cord (Shik et al.,1966; Shik and Orlovsky, 1976). In addition, electrical or chemical stimulation of an area posterior to the peri-brachial part of ventral cuneiform nucleus, or at the dorsolateral end of brachium conjunctivum, an area equivalent to the PPN and including part of the adjacent periaqueductal gray (Garcia-Rill, 1986; Brudzynski et al.,1986; Skinner and Garcia-Rill, 1985; Mogenson et al.,1986), also elicited locomotor activity. Descending efferents from the PPN, now considered as an integral part of the MLR (Garcia-Rill, 1986), may relay signals monosynaptically via nucleus reticularis gigantocellularis to the reticulospinal projections (Garcia-Rill and Skinner, 1985; Orlovsky,1970; Steeves and Jordan,1980; Skinner et al.,1985).

5.2 Functional Connections of The Pedunculopontine Nucleus.

Descending signals from multiple brain sites generally involved in central motor mechanisms may provide triggers for generating rhythmic limb movements by the PPN of the MLR. The linkage from the nucleus accumbens(Nauta et al.,1978) and the subpallidal area (Swanson et al.,1981) to the PPN has led to the suggestion that the PPN may have a role in funnelling signals from the basal ganglia to the spinal cord (Swanson et al.,1985; Mogenson,1986). A crude topographical organization of the subpallidal projection to the PPN has also been identified. Thus, from the substantia innominata, neurones project to the ventral parts of central gray and to the PPN, while the neurones from the lateral preoptic-lateral hypothalamic areas project to medial central gray, sparing most of the PPN and superior colliculus (Swanson et al.,1985).

The functional linkage of these basal forebrain structures with PPN was supported by some recent neuropharmacological experiments. Injection of amphetamine into accumbens releases dopamine from the mesolimbic dopaminergic afferent terminals in this nucleus, producing a hyperkinetic effect which is accompanied by a massive increase in locomotor activity in the animals (Brudzynski and Mogenson, 1985). Procaine, a reversible neuronal blocker (Richards, 1982; Skou, 1961; Seeman,1972; Taylor, 1959) injected into the PPN, markedly reduced the amphetamine-

induced hyperkinetic activity. This suggests that dopamine receptor stimulation in the accumbens activates the descending accumbens pathways to influence the PPN (Brudzynski and Mogenson, 1985)to elicit locomotor movement. Since the nucleus accumbens projects its massive GABAergic efferents to the ventral pallidum and the subpallidal region (Nagy et al.,1978,; Ribak et al.,1979), it is possible that through the subpallidal region accumbens activation is expressed as locomotor activity. Thus, by blocking the GABAergic receptors on the subpallidal neurones with picrotoxin, locomotor activity increased significantly (Mogenson and Nielsen, 1984). This picrotoxin-induced increase in locomotor activity can be blocked by injecting procaine into the zona incerta where the subpallidal-PPN neural pathway passes (Mogenson et al.,1985). These studies, therefore, showed a descending influence of accumbens efferents via the subpallidal region to activate PPN of the MLR which contribute to movement.

Apart from this subpallidal-PPN pathway, other afferent inputs to the PPN may also contribute to the initiation of locomotor responses. These inputs come from: i) pre-motor and motor cortex (Moon-Edley and Graybiel,1983; Hartmann von Monakow et al.,1979); ii) the substantia nigra pars reticulata (Beckstead, 1983; Garcia-Rill et al.,1983; Hopkins and Neissen, 1976; Nauta et al.,1978; Noda and Oka,

1984; Saper and Loewy, 1982; Wright and Arbuthnott, 1980; Sugimoto and Hattori,1984); iii) the subthalamic nucleus and the zona incerta (Jackson and Crossman, 1981; Moon-Edley and Graybiel,1983; Hammond et al.,1983; Nauta and Cole,1978; Ricardo, 1983; Swanson et al.,1983). A number of these extrapyramidal brain sites is connected reciprocally with the PPN. The ascending efferent fibres from the PPN terminate in the substantia nigra pars compacta, subthalamic nucleus, medial pallidal segment, entopeduncular nucleus, thalamus (centrolateral, ventral, centre median, parafasicular and intralaminar nuclei), ventral tegmental area and lateral hypothalamus (Saper and Loewy, 1982; Sugimoto and Hattori, 1984, Philipson,1979). Thus, the PPN may be considered an integral part of the extrapyramidal system.

The precise physiological role of the PPN in orchestrating incoming signals from the globus pallidus, substantia nigra or the subthalamus remains undefined. This reflects, in part, the present lack of detailed knowledge of the neurotransmitter systems which regulate the activity of the PPN. Furthermore, although midbrain and lower parts of the central nervous system are sufficient to generate patterns of locomotor movements in decerebrate animals, the more rostral structures in the striatum are necessary for initiation of locomotor behaviour and spatial orientation (Shik and Orlovsky, 1976; Mogenson, 1984). Hence, as mentioned earlier, considering the fact that

decorticated animals with intact basal ganglia can initiate normal goal-directed locomotor movements, it is possible that limbic pallidal efferents can act through MLR to elicit locomotor activity without a direct input from the motor cortex (Mogenson, 1984). Furthermore, considering the massive limbic afferent inputs to the nucleus accumbens, it is conceivable that limbic signals influence somatomotor mechanisms through the accumbens->subpallidal->PPN-> spinal generator pathway (Mogenson, 1984).

METHODS AND PROCEDURES

1. Extracellular Single Unit Recordings and Electrical Stimulation

Experiments were performed on male Wistar rats weighing 250-330 g. The animals were anaesthetized with urethane (1.5g/kg, i.p.) and placed in a Kopf stereotaxic apparatus. Rectal temperature was monitored with a Yellow Springs Instruments telethermometer and maintained between 36-38 °C with a radiant heat lamp. Stimulating electrodes were positioned stereotaxically, via holes drilled through the skull, to the brain sites ipsilateral to the site of stimulation. The recording electrodes were lowered into the brain by a hydrualic microdrive (1207B, David Kopf Instrument). The stereotaxic coordinates used were obtained from a standard atlas of the rat brain (Pellegrino et al.,1979), with the incisor bar adjusted 5mm above the interaural plane. The coordinates used to reach the different nuclei involved in the following experiments (including those in the locomotor activity assay experiments) are listed in Table 1. The degree of inclination to the saggital plane of the stimulating electrode, (or cannulae which were positioned in the brain sites for microinjection of drugs) is given in brackets.

Extracellular unit activity was recorded with glass microelectrodes which were pulled from Kwik-Fil glass capillary (W-P Instruments, U.S.A.) on a Narishige

Table 1

Stereotaxic coordinates used for the placement of recording and stimulating electrodes, as well as injection cannulae to various nuclei in the rat brain.

	Anterior(A)/ Posterior(P) to the bregma	Lateral to saggital sinus	Depth from surface of cortex
Ventral subiculum of hippocampus	P:3.0-3.2mm	4.8-5.0mm	7.5-8.0mm
Nucleus accumbens	A:3.0-4.0mm	0.9-1.5mm	5.5-8.0mm
VTA	P:2.8mm	1.0mm	8.9mm(14°)
Ventral pallidum	A:1.6-2.0mm	1.5-3.2mm	7.0-9.0mm(24°)
Subpallidal area	A:0.6-1.2mm	1.5-3.2mm	7.0-9.0mm(24°)
Pedunculopontinus nucleus	P:5.2-5.4mm	1.1-1.9mm	6.5-7.5mm

microelectrode puller (Narishige Scientific Instruments Lab., Tokyo, Japan). The microelectrodes were filled with 0.5M sodium acetate containing 2 % Pontamine Sky Blue (Gurr, U.K.). The impedance of the recording electrode was 5-10 megohms, measured with 1 kHz sine wave. Action potentials recorded from single neurones were fed into a differential AC preamplifier (PBA-1; Federick Haer) and were displayed on a dual-beam storage oscilloscope (5112; Tektronix). Photographic records were obtained from the storage oscilloscope with a Tektronix C-12 oscilloscope camera using Polaroid films. Amplified signals were also fed into an audio monitor (Grass AM-7) and a window discriminator (Federick Haer). Discrete square pulses corresponding to individual spikes were generated by the window discriminator and were sampled on-line by a PDP 11/44 (Digital Equipment Corp.) or an IBM-PC computer. Peristimulus time histograms were generated on a video terminal with data analysis performed off-line.

Concentric bipolar electrodes(NE-100, Rhodes Medical Instruments) having a tip separation of 0.5mm were used for electrical stimulation of the brain. Stimulation was monophasic square-wave pulse of 0.15-0.2 ms duration with a current intensity range of 300-800 uA. The stimulating pulses were generated by a Grass S44 stimulator coupled to a Grass stimulation isolation unit(SIU 5).

2. Iontophoretic Application of Drugs and Neurotransmitter Substances

A single micropipette assembled in parallel with a five-barrel micropipette was used for simultaneous recording and iontophoretic application of drugs and neurotransmitter substances. The multibarrel micropipette blanks were made by binding Kwik-Fil filament-filled capillary (W-P Instrument, U.S.A.) with heat-shrink tubing and superepoxy glue (Elmer's, Borden Chemical, Toronto). The five-barrel microelectrodes were pulled by a Narishige microelectrode puller, accompanied by a 240° twist during the pulling process. Tips of the multibarrel pipette were broken back to an overall average size of 5 um. The barrels were filled with the following compounds (or with the vehicle in which the compound was dissolved for control tests): dopamine hydrochloride (1 M solution containing 0.4 mg/ml ascorbic acid in double-distilled water, pH adjusted with 0.1 M NaOH to 4.0), L-monosodium glutamate (0.5 M solution, pH 8.0), glutamic acid diethyl ester hydrochloride (0.5 M solution, pH 4.0), trifluoperizine dihydrochloride (0.05 M solution in 0.5 M tartaric acid, pH 4.0), or sodium chloride (1M solution, for use in current balancing). All drugs were obtained from Sigma, St. Louis, Mo. except trifluoperizine (from Smith, Kline and French, Philadelphia, PA, U.S.A.). Stock solutions of the drugs were stored at -40° C until use. The solutions were centrifuged before being used to fill the

multi-barrel micropipette. The drug-filled multi-barrel micropipette was assembled in parallel under a microscope with a single-barrel recording electrode whose shaft had been bent to 20° by a small candle flame (Crossman et al.,1973) The distance between the two microelectrode tips was 10-15 um.

Iontophoretic currents were delivered by a Dagan 6400 iontophoretic current generator. Except for glutamate, which was ejected by a negative cathodal current, all other compounds were ejected by a positive anodal current during an experimental test. A retaining current of opposite polarity (1-5 nA) to the charge of the compound was used for drug retention.

3. Identification of Orthodromic Responses

Peristimulus time histograms (PSTH) were computed from the recorded inter-spike and inter-stimulation intervals using a cross-correlation algorithm. The number of stimulus presentations used to compile the PSTH was governed by the baseline firing rate of the neurone determined during the sampling of its activity. For the spontaneously active neurones, usually over 1500 inter-spike intervals were collected before sampling was terminated. Significant changes in activity of neurones following stimulations were identified and quantified by comparing the height of each 1 ms post-stimulus bin of the PSTH with the average height of

the bins 100ms before the stimulus. The boundaries of possible periods of significant response were defined by the consecutive bins with mean height significantly different from the baseline mean. The beginning of an excitatory response was defined as the time of the first of 5 consecutive bins with height that were more than one standard deviation from baseline mean. The response and baseline samples were assumed to be normally distributed. The end of the boundary of an excitatory response was similarly defined as the time of the first of 5 consecutive bins with heights that were within one standard deviation from the baseline mean. Since the probability of a 1 ms bin with height above one standard deviation from the baseline mean is 0.16 [i.e. (1-0.68)/2], the probability of 5 consecutive bins occurring by chance will be equal to $(0.16)^5$ and thus at 0.0001 level of significance. Likewise, the beginning of an inhibitory response was defined as the time of the first of 5 consecutive bins with heights that were one standard deviation less than the baseline mean. While the end of the inhibitory response was defined by the height of the five consecutive bins which were within one standard deviation from the baseline mean. With the boundaries thus defined, the mean height of the bins within the boundaries were expressed as a percentage change compared to baseline (Yim , 1983). Thus, subsequent changes of this percentage after an experimental treatment can be compared.

4. Experimental Procedures for Studying The Interaction of Hippocampal Input and VTA Input to The Nucleus Accumbens.

A) Electrophysiological responses of neurones in the medial accumbens to hippocampal input were recorded in response to single-pulse stimulation of the ipsilateral ventral subiculum at 0.5-1.5 Hz. The intensity of the hippocampal stimulation (300-800uA)was adjusted to elicit at least one action potential from the accumbens neurones per stimulus pulse.

B) Interaction of the converging inputs from the hippocampus and the VTA to the neurone of the accumbens was investigated by stimulating the VTA with trains of 10 pulses at 10 Hz with the last pulse of each train delivered 40-100ms prior to each single pulse stimulation of the hippocampus. Each train of 10 Hz pulses was delivered at 0.5 Hz to the VTA. The sequence of stimulation by the two stimulators was programmed by a digital timer (Devices, Medical Systems Corp.).

Comparison of responses before and after VTA stimulation or drug application was based on peristimulus time histograms compiled from exactly the same number of stimulus presentations. The ratio of the mean height of the bins in the period of the elicited response to that of the base-line was computed for each peristimulus time histogram. A change of 30 or more percent of the elicited responses following

VTA conditioning stimulation or drug application was considered a significant change. The level of significance in this percentage change in mean bin height ($p<0.001$, paired t-test) was established in a series of preliminary experiments in which a comparison was made between the mean bin height of the excitatory responses of 58 accumbens neurones to that of the attenuated excitatory responses after a minimally effective current was delivered to the VTA.

5. Identification of Antidromic Responses

Criteria for antidromic response of the accumbens neurone to either pallidal, accumbens or pedunculopontine nucleus stimulation were:

A) stability of the onset latency at threshold stimulation,

B) faithful responses to high rates of stimulation (e.g. above 200Hz) as tested by pair-pulse stimulation and,

C) collision of the antidromic response with an orthodromically travelling action potential generated by a spontaneously discharging neurone (Fuller and Schlag, 1976; Lipski, 1981). Criterion C) was determined by using a Schmitt trigger circuit which allowed the stimulator to be triggered by a spontaneously active spike. A variable delay was introduced between the arrival of the spontaneous spike

and the delivery of the stimulus. If the delay interval was equal to or less than the conduction time of the orthodromically travelling spike, collision of the elicited spike occurred and the response was considered as an antidromic response (Fuller and Schlag,1978).

Another approach was used to determine whether incoming hippocampal signals to silent accumbens neurones directly relayed to ventral pallidal or subpallidal area (VP or SP). A stimulation pulse was first delivered to the hippocampus by one stimulator (S1) to activate the accumbens neurone synaptically. Following a short period of delay another stimulation pulse was delivered by a second stimulator (S2) to the VP or SP regions to elicit antidromic response in the same accumbens neurone. When the delay interval of S1 and S2 were in the time range where responses evoked by S1 fell within the critical delay period, the synaptically evoked excitatory response of the accumbens output neurone "collided" with the antidromic response elicited by S2 (see Fig. 19). The critical delay period of the accumbens neurone was equal to the conduction latency of the synaptically elicited spike plus its refractory period, which excluded the time for invasion of the soma. Thus, with this approach it was possible to deduce electrophysiologically whether a neural projection from the hippocampus to the accumbens output neurone (synaptically activated by S1) connected directly to the VP or SP region (as shown by the collision

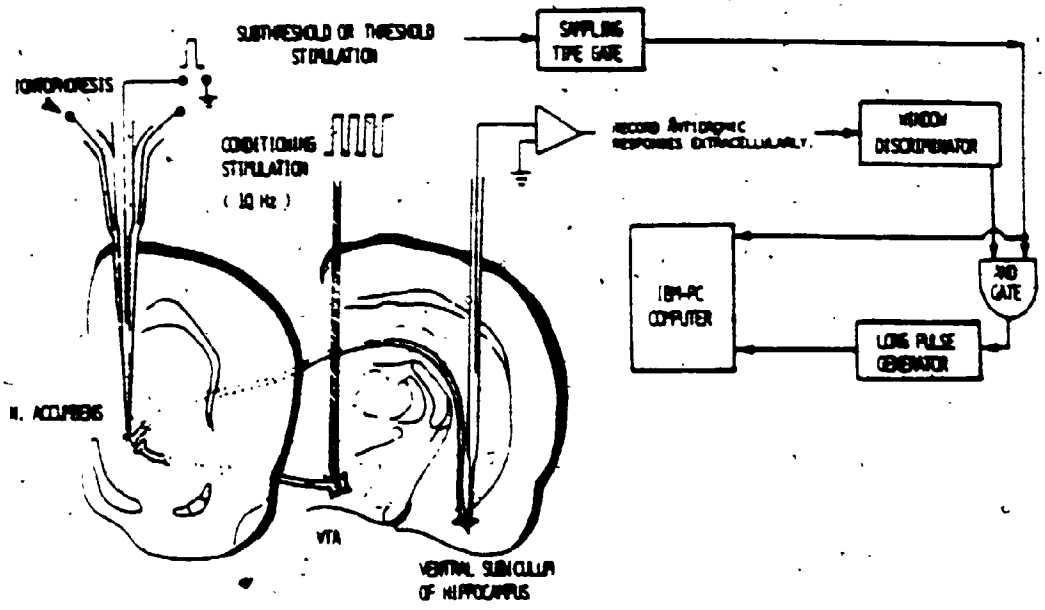
of the synaptically elicited spike by S1 with the antidromically elicited spike by S2).

6. Test of Excitability of Axonal Terminals of Hippocampal-Accumbens Neurones.

A terminal excitability test(Wall,1958; Curtis and Ryall,1967; Lisney,1979; Lovick,1983; Willis et al.,1973) was used to study the effects of dopamine on the axonal terminal of hippocampal-accumbens (HIPP-ACC) neurones. A sampling time gate with adjustable width was arranged in series with a Grass S44 stimulator. Each accumbens stimulation triggered this gate which generated a square wave pulse which, in turn, served as a command to start the IBM-PC computer to count the number of stimuli delivered. The square wave pulse generated by the gate is shown in the upper part of Fig. 2A (designed by Dr. C.Y. Yim, see also Curtis,1973). Antidromic spikes of the HIPP-ACC neurones occurring within the variable gated interval were isolated by a window discriminator (Pederick Haer). The command pulse from the sampling time gate together with the output from the window discriminator, passed through an electronic 'AND' gate to evoke a long duration pulse from a pulse generator. This enabled the computer to count the antidromic responses from each set of 20 stimulation trials on-line (Fig. 2). Antidromic spikes, only with constant latency (or within the tolerable variable latency shift in the range of

FIGURE 2

Block diagram to illustrate the set-up for terminal excitability test. A multi-barrel micropipette assembly, positioned in the medial accumbens was used to elicit antidromic responses of HIPP-ACC neurones which were recorded extracellularly in the ventral subiculum of the hippocampus. A stainless steel concentric bipolar electrode was positioned in the VTA to deliver conditioning pulses in order to activate the mesolimbic dopaminergic neurones. Each accumbens stimulation also triggered a sampling time gate and the pulse generated by this gate started the computer to register the number of stimulations. If an antidromic response, isolated by a window discriminator, occurred at this preset gated interval, a 3 ms long pulse was generated to trigger the computer to count the number of antidromic response and subsequently, compute the firing index (see Methods for details).


SUBTHRESHOLD OR THRESHOLD STIMULATION
SAMPLING TYPE GATE
IONTOPHORESIS
CONDITIONING STIMULATION
(10 Hz)
WINDOW DISCRIMINATOR
IBM-PC COMPUTER
AND GATE
LONG PULSE GENERATOR
N. ACCUMBENS
VTA
VENTRAL SUBICULUM OF HIPPOCAMPUS

0.1-0.2ms), occurring within the adjustable gated period, were sampled. Other spikes which fell outside the gated interval were excluded from sampling.

The accumbens stimulation was delivered through the centre barrel (filled with 4M NaCl solution) of a 5-barrel micropipette assembly (tip size: 10-15um) at 0.6 Hz. The stimulation was generated by a Grass S44 stimulator which was coupled to a photoelectric stimulus isolation unit (PSIU 6) with constant current output. Stimulations consisited of monophasic square pulses(0.15-0.2ms duration)in the current intensity range of 5-200uA . The side barrels of the multi-barrel pippete were filled with the following drugs: dopamine (0.02M prepared in double distilled water, with 0.2mg/ml ascorbic acid added as an anti-oxidant, and pH was adjusted to 4.0; Sigma, Minn.); LY171555 (quinpirole hydrochloride, a selective D-2 agonist, 0.02M, pH4.0, Lilly Co. Minn.), SKF38393 (2,3,4,5 tetrahydro 7,8-dihydroxyl-phenyl 1 H-3-benzazepine, a selective D-1 agonist, 0.02M, pH 4.0, Smith, Kline & French Co., Phild.); sulpiride (a selective D-2 antagonist, 0.1M, pH 5.5, Sigma); and 2% pontamine skyblue in 0.2M sodium acetate. Stock solutions of the drugs were stored at -40° C until use. The drugs were held in the barrels by 5-10nA cathodal retaining current and ejected with anodal current. A barrel filled with 0.9 % NaCl was used for automatic current balancing (Dagan 6400) in order to compensate for the current effects during drug

application (Salmoiraghi and Weight,1965).

A baseline firing index, defined as:

$$\frac{\text{No. of antidromic responses}}{\text{No. of stimulations in each set of 20 trials}} \times 100$$

was determined from the last five to ten sets of stable test trials before each experimental treatment. In preliminary experiments, when the baseline firing index was 50, predominant enhancement of firing index following VTA stimulation was observed. In order to further increase the resolution of the firing index, stimulating current was adjusted to elicit 6-8 antidromic responses in each set of 20 stimulation trials. Thus, stable firing index of 35-40 determined from five to ten sets of stimulation trials was treated as baseline response. The firing index was also computed continuously on-line before, during and after each experimental treatment.

In additional preliminary experiments on 35 cells, a minimally effective current used (200uA)to stimulate the VTA (5 trains of 10 Hz pulses) produced a mean increase of firing index by 100 %(range:71-136%). Since peak responses following each VTA stimulation occurred within the first 5 sets of test trials, the mean values of these post-stimulation responses were used to compare with the mean control values determined from the last 5-10 sets of baseline test trials. A paired-t test showed a significant

increase($t=5.59, p<0.001$) in the post-stimulation firing index. In subsequent experiments involving the iontophoresis of dopamine and its agonists, changes of baseline firing index by 100% or greater were considered as significant changes.

7. Systemic Administration of Haloperidol, Sulpiride or SCH23390

Haloperidol (Haldol; McNeil Lab., Canada)(0.2-0.5mg/kg, i.p.), Sulpiride (20mg/kg,i.p.) or SCH23390 (R-(+)-8-chloro- 2,3,4,5, tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol; Schering-Plough Corp., Bloomfield, New Jersey; suspended in 0.4 % methylcellulose, 6-10mg/kg,i.p.), all dopamine receptor antagonists, were injected intraperitoneally before some recording sessions to block the effects of dopamine released in the central nervous system.

8. Intracerebral Injection of Drugs

In electrophysiological experiments, drugs were directly injected intracerebrally via a 30 gauge stainless steel cannula positioned stereotaxically by a Kopf electrode holder. The drugs were injected through PE-10 tubing connected to the injection cannula using a Hamilton microsyringe in volumes of 0.2-0.5 ul. Drug compounds that were injected in this manner into the medial accumbens were: GDEE (10-20 ug/0.5-0.1ul in saline); LY171555 (2.5 ug/0.2 ul

in saline); SKF38393(2.0 ug/0.2ul saline).

Neurotoxins

8.1 6-Hydroxydopamine Lesion of The VTA Mesolimbic Dopaminergic System

In pentobarbital-anaesthetized (60 mg/kg,i.p. Somnotol, MTC Pharmaceutical, Hamilton, Ontario) rats, 6-hydroxydopamine hydrobromide (8 ug in 1 ul, dosage expressed as the free base in saline containing 0.2 mg/ml ascorbic acid added as anti-oxidant), a neurotoxin for catecholaminergic neurones, was injected unilaterally into the VTA through a 30-gauge stainless steel cannula which was connected to a Hamilton microlitre syringe by a PE-10 polyethylene tubing (Clay Adamson Parsppary, N.J.). The 1 ul 6-hydroxydopamine was injected over a period of 3 min and a 5 min diffusion time was allowed before removal of injection cannula. These animals were first pretreated with Pertofane(desipramine hydrochloride; Ciba-Geigy, Canada, 25 mg/kg,i.p.) 0.5-1 hr prior to the injection of 6-hydroxydopamine in order to prevent the uptake of 6-OHDA by noradrenergic neurones(Roberts et al.,1975). Following the 6-OHDA treatment, these animals were kept with food and water available ad libitum for 2 days or 7-9 days before a recording session.

8.2 Ibotenic Acid Lesion of The Nucleus Accumbens

Ibotenic acid, an axon-sparing neurotoxin, was

microinjected into the medial accumbens of anaesthetized rats, 7-9 days prior to each electrophysiological recording session (Kohler and Schwarz, 1983). The unilateral accumbens injection of ibotenic acid was performed in rats under pentobarbitol anaesthesia (Somnotol, 60mg/kg, i.p.). Ibotenic acid(3ug/0.5ul in phosphate buffered saline, pH 7.4) was injected through a 30 gauge stainless steel cannula which was connected to a Hamilton microlitre syringe by a PE-10 polyethylene tubing (Clay Adams, Parsippary, N.J.) into the medial accumbens at a rate of 0.1ul/min. After the injection, the injection cannula was left in the accumbens for an additional 5 min to avoid backflow along the cannula track. The rats were returned to their home cage for 7-9 days with food and water available ad libitum before being used in electrophysiological recording experiments.

9. Experiments Examining Locomotor Activities Following Intracerebral Injections of Drugs

The experiments were performed in male Wistar rats weighing 225-250 g at the time of surgery. During the surgery, the animals were first anaesthetized with sodium pentobarbital (60mg/kg, i.p.,Somnotol, MTC Pharmaceuticals, Hamilton, Ont.) and placed in a Kopf stereotaxic frame with the incisor bar positioned at 5 mm above the interaural line. Guide cannulae (14.45mm), constructed from 23-gauge hypodermic needle tubings, were implanted stereotaxically into the brains bilaterally in 3 groups of rats:

A. Ventral subiculum of the hippocampus (HIPP) and medial accumbens.

B. HIPP and subpallidal area.

C. HIPP and pedunculopontine nucleus.

The guide cannulae were inserted into the brain 1.25mm above the target site and were subsequently secured onto the skull by jewelry screws and dental acrylic (Hygenic Co., Akron, OH.). After the surgery, stainless steel wires, cut into the same length as the cannulae (14.45 mm) ware inserted into the guide cannulae to preserve patency. To prevent infections, Pen-Di-Strep (0.15ml i.m. Rogar/STB Div. BTI products Inc., London, Ont.) was administered immediately after the surgery. The animals were given 1 week for recovery from the surgery, followed by 3-4 days of adaptation in an apparatus for testing locomotor activity (Optovarimax-3, Columbus Instruments International Corp., Columbus, OH). The total adaptation period for each animal was 30 min per session each day. Following each exparimental session, the animals were returned to their home cage with food and water available ad libitum and kept in a 12 hour light: dark cycle.

Locomotor activity before and after intracerebral microinjection of drugs were recorded by the Optovarimex-3 activity apparatus which has an overall dimension of 42.2X42.2X20.3 cm. The apparatus was housed within a sound-

proof illuminated enclosure (by one 15 W light bulb) with an inner dimensions of 86X74X88 cm. An electric fan provided air circulation and background noise. The locomotor activity of the animals were tested at 0900-1200 hours each morning. The locomotor activity was measured from the accumulated number of interruptions individual infrared beams from two arrays of 15 infra-red lights located on the X- and Y-axis inside the activity box (expressed as counts per unit time). Horizontal locomotor activity were automatically summed up in 1-min periods for 15 min before (baseline) and 15 min after (experimental)drug injections. The accumulated counts were printed by Printing Counter-800 (Columbus Instruments International Corp., Columbus, OH.).

Intracerebral injection of drugs was performed via a 30 gauge stainless-steel (15.7mm) cannula connected by PE-10 polyethylene tubing (Clay Adams, Parsippary, N.J.) to a Hamilton microsyringe. All drugs were injected at a rate of 0.1ul/30s and a total volume of 0.2ul was injected into each site. After the injection the cannula was allowed to remain in the brain for one more minute to prevent backflow of drugs before the animal was to put back into the activity box. Recording of post-drug response began 5 min after drug injection.

N-methyl-D-aspartic acid (NMDA) was injected in a dose of 0.5 ug/0.2 ul into the ventral subiculum of the hippocampus. Elicited locomoter responses by NMDA injection

into the hippocampus were further assessed by prior injection of:

1. LY171555, a dopamine D-2 agonist (1-4 ug/Ø.2ul), into the medial nucleus accumbens.
2. Nipecotic acid, a GABA uptake inhibitor (1-4 ug/Ø.2 ul saline, Sigma), into the subpallidal area.
3. Procaine hydrochloride, a neural transmission blocker (30ug/Ø.2ul; Sigma), into the region of the subpallidal area or the pedunculopontine nucleus.
4. Saline as a control (Ø.2 ul).

Mean locomotor response obtained between 5 to 10 min during the post-injection period was expressed as a percentage of each individual rat's own last 5 min baseline pre-injection locomotor response. The influence of different drugs in various dosages injected into the accumbens on the NMDA-induced locomotor response was assessed statistically by a one-way analysis of variance, followed by post-hoc Newman-Keuls test. All paired-wise analyses were completed using Student 't'-test.

10. Histological Verification of Stimulation, Recording and Cannula Sites

At the end of each electrophysiological experiment, stimulus sites were marked by an iron deposit by passing 10 uA anodal current through the stimulating electrode for 1 min. Recording sites were marked by expelling Pontamine Sky

Blue as an anion with a cathodal current of 10 uA for 10 min. The animal was injected with an overdose of urethane, perfused transcardially with saline and then followed by a 3% solution of potassium ferricyanide in buffered formalin. A ferri-ferrocyanide redox reaction produced a Prussian Blue spot marking the stimulation-electrode tip position in the tissue. Likewise, cannula sites for rats in the locomotor activity experiments were located with the above perfusion methods in the animals which were previously overdosed with urethane. The degree of spreading of the drugs injected intracerebrally was assessed by injecting an equal volume of Pontamine Skyblue (0.2ul) into the brain sites before sacrificing. Buffered formaline was used for tissue perfusion without adding the potassium ferricyanide. The brain was subsequently removed and fixed in formalin for 24 hr. Frozen coronal sections were then mounted on gelatinized glass slides and stained with Neutral Red or thionin for histological verification of the stimulation, recording or cannula sites.

RESULTS

1.0 Single Unit Recordings from the Nucleus Accumbens

1.1 Electrophysiological Responses of Accumbens Neurones to Hippocampal Stimulation.

Stimulation of the ipsilateral ventral subiculum of the hippocampus activated both silent and spontaneously active neurones in the medial, but not lateral, nucleus accumbens of 58 rats. The majority of the neurones in this region of the accumbens were silent and were identified by their discharges only when the hippocampus was stimulated.

Along the medial portion of the nucleus accumbens, 109 silent neurones were identified electrophysiologically (Fig. 3). These neurones were normally quiescent but occasional spontaneous discharges (<one spike per second) were observed. Single pulse stimulation of the hippocampus elicited a single spike or occasionally a burst of 2-3 spikes from all 109 silent neurones tested (Fig. 4). The onset latency of excitation was short, ranging from 6-15 ms (mean, 11 ms). The duration of the excitatory responses was usually short (mean, 11 ms) (Table 2) and so the post-stimulus histogram had a narrow peak. Also in the medial nucleus accumbens, 77 spontaneously active neurones with slow firing rates between 3 to 6 spikes/s, were identified (Table 2). Single pulse stimulation of the hippocampus excited all of these spontaneously active neurones. The onset latency of excitation ranged from 8 to 20 ms (mean, 14

FIGURE 3

Recording sites shown on coronal sections of the brain (After Pellegrino et al.,1979).

A: Closed triangles (▲) indicate the locations of the excitatory responses of the spontaneously active neurones to hippocampal stimulation. Open triangles (△) indicate the locations of the inhibitory responses of the spontaneously active neurones to hippocampal stimulation.

B: Closed circles (●) indicate the locations of the excitatory responses of the silent neurones to hippocampal stimulation.

ACC, nucleus accumbens;

CA, anterior commissure;

CC, corpus callosum;

CPU, caudate putamen complex;

DBB, diagonal band of Broca;

LS, lateral septum.

(Calibration bar: 1 mm.)

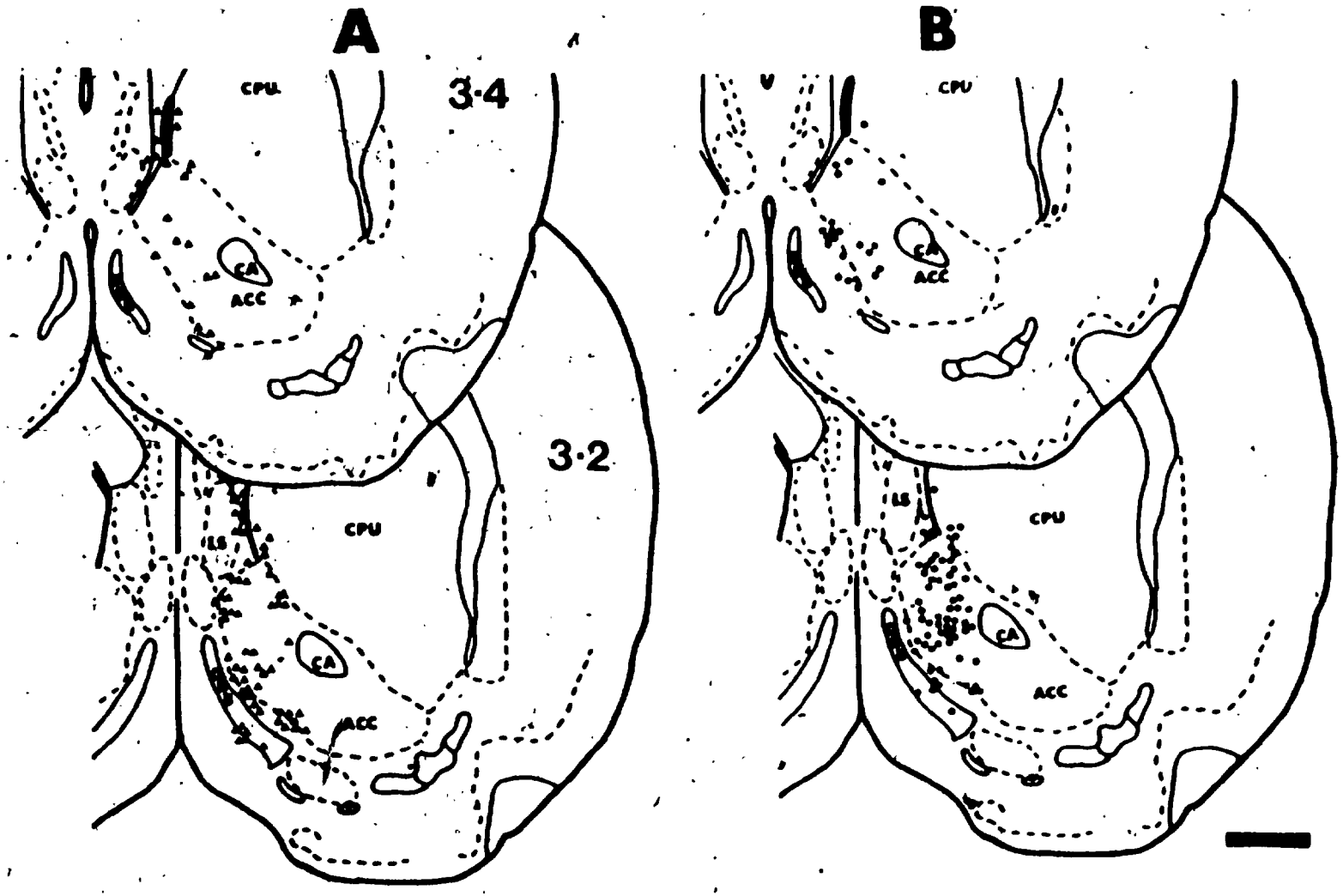

A
B
CPU
3·4
3·2
CA
ACC
LS
CPU
CA
ACC
LS
CPU
CA
ACC

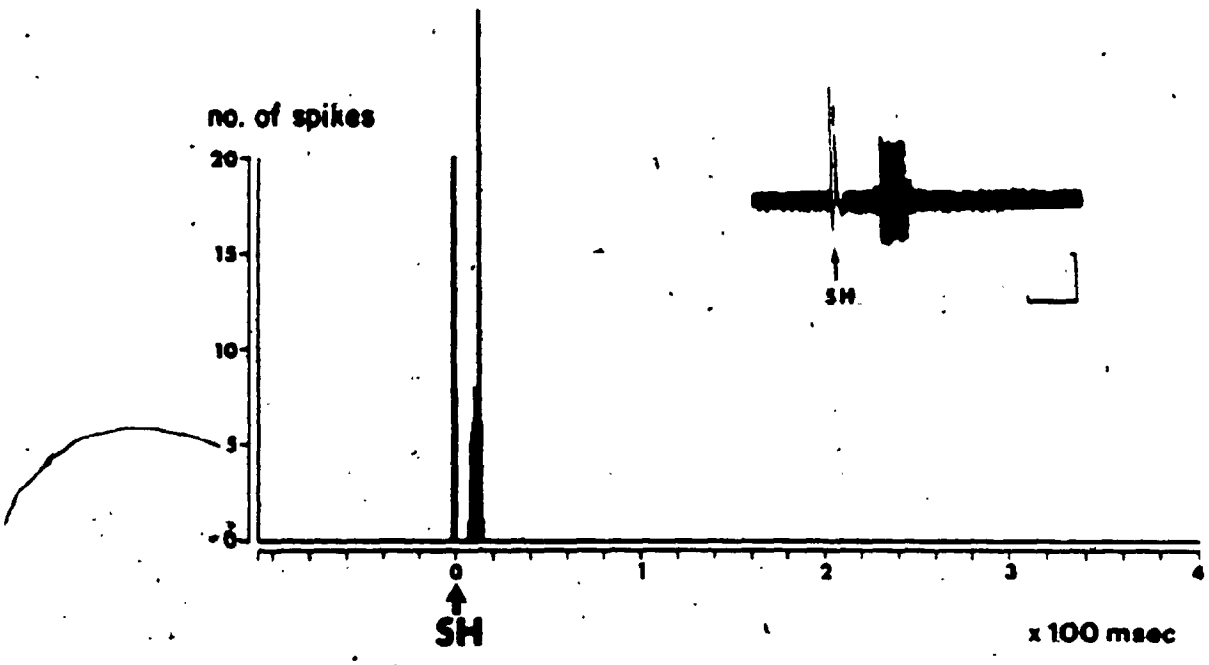
Table 2

Responses of the accumbens neurones to hippocampal stimulation.

	Silent Neurones		Spontaneously Active Neurones	
Location in the nucleus accumbens	medial portion	dorso-medial border	medial portion	ventral portion
Types of responses	excitation	inhibition	excitation-inhibition	inhibition
Mean firing rate (Hz)	0 - <1	8 - 12	3 - 6	25 - 40
Latency of excitation and inhibition (M.±S.E. ms)	11 ± 0.4	14 ± 1.3	13 ± 1.1	13 ± 3
Duration of excitation and inhibition (M.±S.E. ms)	11 ± 0.6	173 ± 34.6	17 ± 1.4	130 ± 28
Total no. of neurones observed	109	26	77	50

FIGURE 4

A peristimulus time histogram showing a typical response of a silent accumbens neurone to hippocampal stimulation. Current pulses of 300uA for 0.15 ms at 0.5 Hz were delivered to the ventral subiculum of the hippocampus at the time indicated by the arrow (SH). The histogram was compiled from 150 sweeps. Note the absence of background spontaneous activity. The latency of the excitatory response was 8 ms and the duration 9 ms. Inset shows the excitatory response photographed from the oscilloscope recording. The record is of 10 sweeps and the arrow (SH) indicates the time of stimulation. Calibration: 100uV and 10ms.


no. of spikes
20
15
10
5
0
0
1
2
3
4
SH
x 100 msec
SH

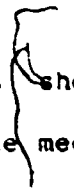
ms) and lasted for a mean duration of 17 ms. Frequently this short period of excitation was followed by a period of inhibition which lasted for 20-50 ms (Fig. 5B).

The results differed for neurones at the dorsal and ventral borders of the nucleus accumbens. In the dorso-medial nucleus accumbens and in the area adjacent to the lateral septum, recordings were made from 26 spontaneously active neurones (Fig. 3A), which discharged with a moderately fast frequency of 8-12 spikes/s (Table 2). When the ventral subiculum of the hippocampus was stimulated by single pulses at 1.5 Hz, a prolonged inhibition resulted (Fig. 5A). The mean onset latency of the inhibition was 14ms and it lasted for a mean duration of 173 ms (Table 2). Along the ventral border of the nucleus accumbens and the olfactory tubercle, 50 fast firing neurones were recorded. These neurones had a discharge rate greater than 20 spikes/s. Single pulse stimulation of the hippocampus inhibited these neurones (Fig. 5C). A few of the fast firing neurones in the vicinity of the diagonal band of Broca, however, were also excited by hippocampal stimulation (Fig.3A).

1.2 Modification of Excitatory Responses to Hippocampal Stimulation by Stimulating the Ventral Tegmental Area.

The excitatory responses of the silent and the spontaneously active neurones in the medial accumbens were attenuated by stimulating the VTA with a train of 10 pulses prior to single pulse stimulation of the ventral subiculum

FIGURE 5



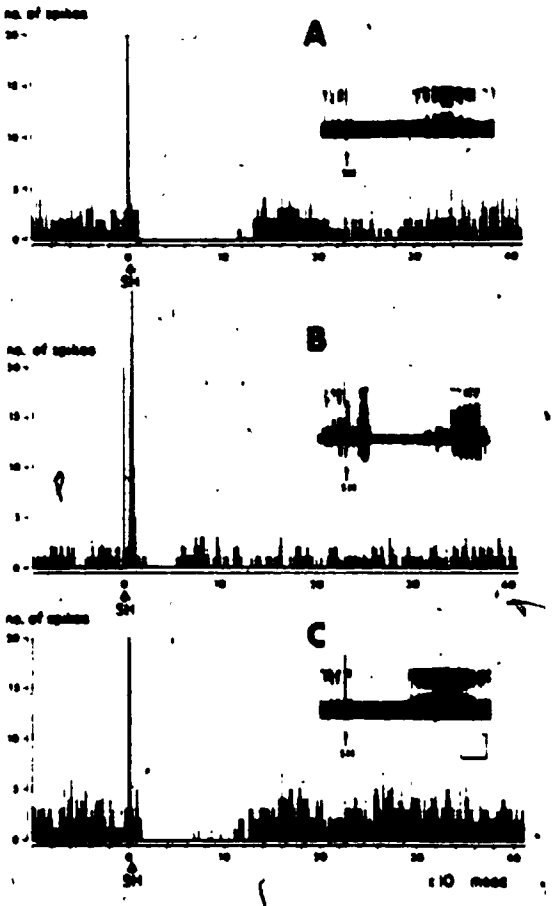
Peri-stimulus time histograms showing 3 types of responses recorded from neurones in the medial nucleus accumbens to hippocampal stimulation.

A: Inhibition of a spontaneously active neurone located in the dorso-medial region of the nucleus accumbens.

B: Excitation of a spontaneously active neurone located in the medial nucleus accumbens proper.

C: Inhibition of a fast-discharging neurone located in the ventral accumbens bordering the olfactory tubercle.

For A and C the current intensity was 500uA and the pulse duration 0.15 ms at 1.5 Hz. The histograms for these neurones were compiled from 250 sweeps. Response in B was to single-pulse stimulation of the hippocampus at 400uA, 0.15ms duration and 0.5 Hz. The histogram for B was compiled from 150 sweeps. Insert shows the responses photographed from the oscilloscope recording. Each record is from 10 sweeps and the arrow (SH) denotes time of stimulation. Calibration: 100uV and 50ms for A and C; and 100uV and 20 ms for B.


A
B
C
SH
10 msec

of the hippocampus. In preliminary experiments intervals of 20, 50, 100 and 200 ms between VTA conditioning stimulation and hippocampal stimulation produced similar attenuating effects. When the VTA conditioning stimulation was a train of 5 pulses there was partial attenuation (10-15%), whereas single-pulse VTA conditioning stimulation resulted in no attenuation of the activation of accumbens neurones by hippocampal stimulation (Fig. 6). Therefore, in the main series of experiments it was decided to use a 100-ms interval to separate VTA conditioning stimulation (10 Hz pulses) and hippocampal stimulation (single pulses).

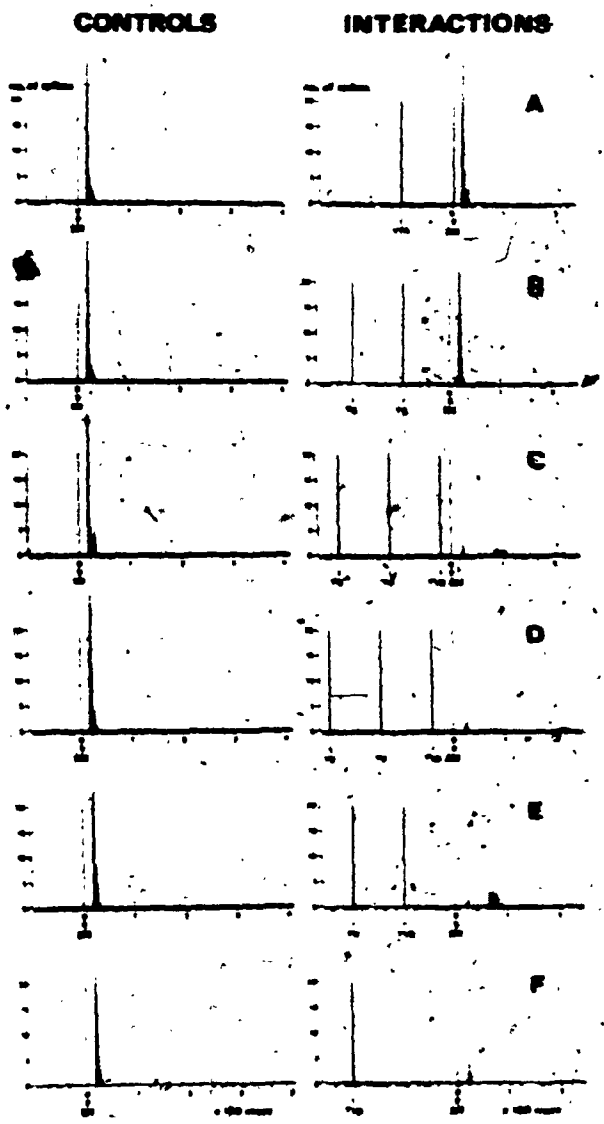
Of the 46 silent neurones tested, the excitatory responses of 41(89%) of them were attenuated by VTA stimulation. As mentioned in the Methods (section 5), only excitatory responses from accumbens neurones which were attenuated by 30% or more were considered as significant attenuation. In ten neurones tested, this attenuation was graded in that a higher current (e.g. 500uA) delivered to the VTA attenuated the excitatory responses of the silent neurones more than a moderate current (e.g. 300uA). Of the 30 spontaneously active neurones tested, the excitatory responses of 26 (87%) to hippocampal stimulation were attenuated by the VTA stimulation and 4 (13%) were not affected (Table 3). On the other hand, the inhibitory responses of spontaneously active neurones along the dorso-

FIGURE 6

Peristimulus histograms showing the effects of different combinations of inter-stimulus parameters on the interaction of hippocampal afferent and the VTA afferents in a nucleus accumbens neurone.

A: The control shows an excitatory response of an accumbens neurone to single-pulse stimulation of the ventral subiculum of the hippocampus indicated by the arrow SH (500uA, 0.15ms duration, 0.6 Hz). Interaction with single-pulse stimulation of the VTA (200uA, 0.15 ms, 0.6 Hz) delivered at 100ms prior to hippocampal stimulation produced no effect on the excitatory response.

B-F: Conditioning stimulation of the VTA with trains of 5 pulses 100ms prior to single-pulse stimulation of the hippocampus (SH) did not produce noticeable changes in the excitatory responses of the accumbens neurone. V4 and V5 represent the last of the five pulses delivered to the VTA. Following recovery in each case, conditioning stimulation of the VTA with trains of 10 Hz pulses ending at C) 20ms, D) 40 ms, E) 100ms and F) 200ms before single pulse stimulation of the hippocampus markedly attenuated the excitatory responses of the accumbens neurone. V8,V9, and V10 represent the last 3 of the 10 pulses delivered to the VTA. All histograms were compiled from 150 sweeps.


CONTROLS
INTERACTIONS
A
B
C
D
E
F

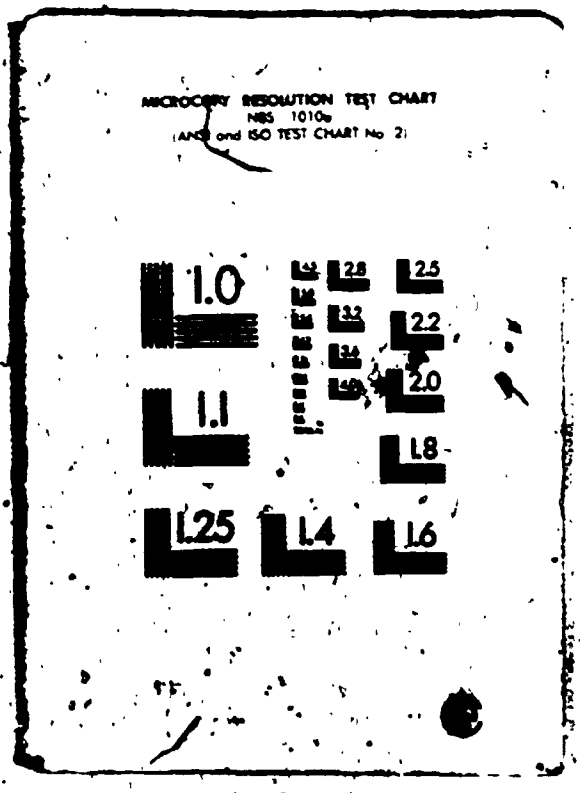

MICROCOPY RESOLUTION TEST CHART
NBS 1010a
(ANSI and ISO TEST CHART No. 2)
1.0
1.1
1.25
1.4
1.6
2.8
3.2
3.6
4.0
2.5
2.2
2.0
1.8

TABLE 3

Effects of VTA conditioning stimulation, iontophoretic application of dopamine, or GDEE on the excitatory responses of accumbens neurones to hippocampal stimulation.

	Conditioning VTA stimulation	Iontophoretic application of dopamine	Conditioning VTA stimulation, and iontophoretic application of dopamine.	Iontophoretic application of GDEE
	n = 76	n = 45	n = 10	n = 10
Attenuation of excitatory responses of accumbens neurones to hippocampal stimulation.	67 (41+26)	40 (29+11)	9 (6+3)	5 (4+1)
No change	9 (5+4)	5 (4+1)	1 (1+0)	5 (4+1)

The first number in brackets indicates the number of silent neurones tested, and the second number indicates the number of spontaneously active neurones tested.

Only excitatory responses from accumbens neurones which were attenuated by 30% or more were considered (See Methods section).

medial border (Fig.5A) and the ventral border (Fig.5C) of the nucleus accumbens to hippocampal stimulation were not affected by VTA conditioning stimulation. Stimulation of the VTA evoked antidromic responses in 4 accumbens neurones and orthodromic excitation in 10 accumbens neurones. For each of these accumbens neurones the excitatory response to hippocampal stimulation was attenuated by conditioning VTA stimulation.

1.3 Modification of the Excitatory Responses to Hippocampal Stimulation by Iontophoretic Application of Dopamine or Glutamic Acid Diethyl Ester.

The excitatory responses of 40 (89%) accumbens neurones to stimulation of the ventral subiculum of the hippocampus were markedly attenuated by continuous iontophoretic application of dopamine (5-30 nA during the entire on-line sampling period, up to 2 min). The excitatory responses of only 5 (11%) of these neurones were not affected by dopamine (Table 4). Criteria for attenuation were: i) reversibility, ii) reproducibility and iii) the effect not being mimicked by control currents.

For 10 accumbens neurones activated by hippocampal stimulation, a comparison was made of the attenuating effects of conditioning VTA stimulation and of the iontophoretic application of dopamine. The excitatory responses of 9 of these neurones were attenuated first by trains of 10 pulses delivered to the VTA. Upon full recovery

TABLE 1

Attenuation by VTA conditioning stimulation of the excitatory responses of accumbens neurones to hippocampal stimulation in rats treated 6-hydroxydopamine (n=7) or haloperidol (n=8).

	Silent Neurones			Spontaneously Active Neurones		
	No treatment	+6-OHDA	+Haloperidol	No treatment	+6-OHDA	+Haloperidol
Total no. of accumbens neurones excited by hippocampal stimulation.	46 (100%)	25 (100%)	41 (100%)	30 (100%)	18 (100%)	18 (100%)
No. of excitatory responses attenuated after VTA stimulation.	41 (89%)	6* (24%)	17** (41%)	26 (87%)	1Δ (6%)	6ΔΔ (33%)
No. of excitatory responses NOT affected by VTA stimulation.	5 (11%)	19* (76%)	24** (59%)	4 (13%)	17Δ (94%)	12ΔΔ (67%)

* denotes χ^2 =27.8 and p< 0.001. Δ denotes χ^2=26.9 and p < 0.001. **denotes χ^2=22 and p < 0.001. ΔΔ denotes χ^2 =14.4 and p< 0.001 compared to the number of neurones from rats receiving no prior drug treatment.

FIGURE 7

Peristimulus time histograms showing the attenuation of the excitatory response of an accumbens neurone to hippocampal stimulation by VTA conditioning stimulation and by iontophoretic application of dopamine. Note that the neurone is silent for relatively long periods of time. All histograms were compiled from 150 superimposed sweeps.

A: Excitatory responses of the accumbens neurones to single-pulse stimulation (400uA, 0.15ms duration at 0.5 Hz).

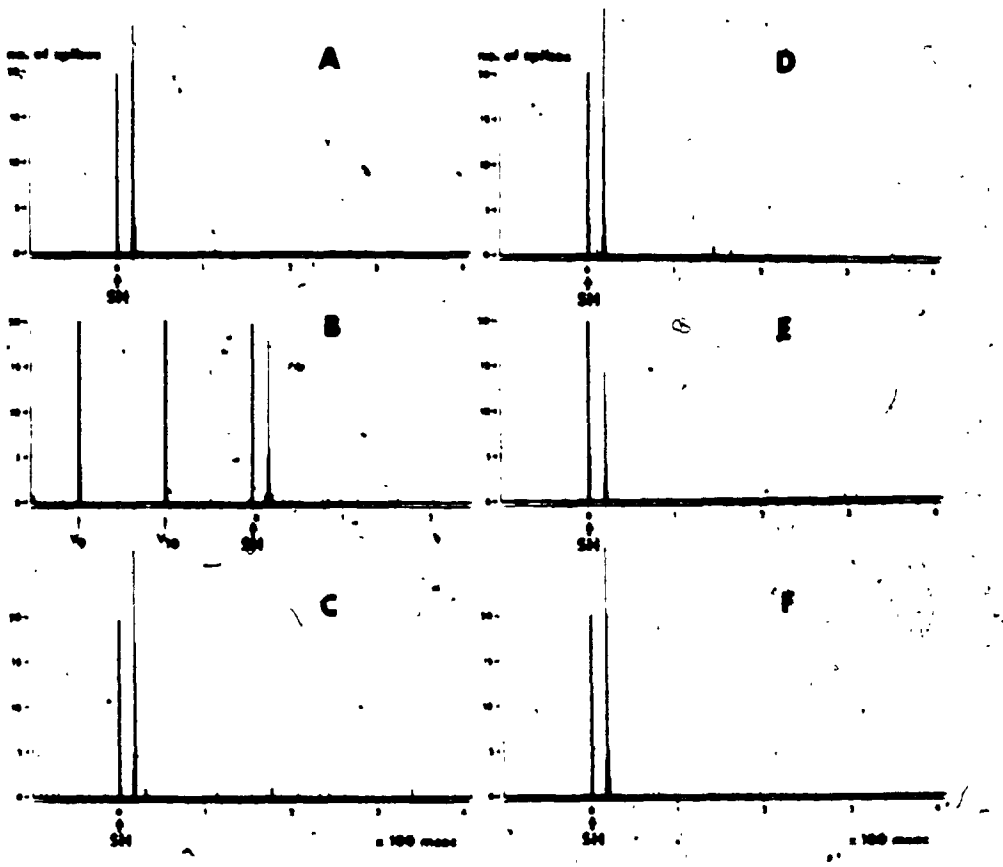
B: Attenuation of these excitatory responses of the accumbens neurone to hippocampal stimulation after stimulation of VTA by a train of pulses (+300uA, 0.15 ms at 10 Hz). V9 and V10 represent the last two of the 10 pulses delivered to the VTA before a single-pulse stimulation of the hippocampus (SH).

C: Recovery of the excitatory response of this neurone to control level.

D: Excitatory response of this neurone to hippocampal stimulation in a control test when +30nA Na was applied iontophoretically. There was no change in the excitatory response as compared to A.

E: Attenuation of the excitatory responses of this accumbens neurone to hippocampal stimulation when +15 nA dopamine was iontophoretically applied to the accumbens.

F: Full recovery of the excitatory response to control level had occurred 12 min after termination of the iontophoretic application of dopamine.


A
D
B
E
C
F
SH
SH
SH
SH
SH
SH

to control response, the iontophoretic application of dopamine also attenuated the excitatory responses of the same 9 neurones to hippocampal stimulation. Figure 7 illustrates such responses in a silent neurone. The baseline firing rate of spontaneously active accumbens neurones was reduced not more than 10-15 % by VTA conditioning stimulation or by the iontophoretic application of dopamine whereas the excitatory responses to hippocampal stimulation were reduced by 40-60 %. Both baseline firing and the excitatory response of accumbens neurones were suppressed completely only when higher stimulating current was delivered to VTA or higher iontophoretic current was used to apply dopamine. Iontophoretically applied dopamine consistently produced a prolonged attenuation of the excitatory responses of the accumbens neurones to hippocampal stimulation. After the termination of iontophoretic application of dopamine, it took 10-20 min for the excitatory responses of the accumbens neurone to hippocampal stimulation to return fully to the control responses (Fig. 8). This prolonged attenuation of the excitatory responses of accumbens neurones to hippocampal stimulation was also observed when the VTA was stimulated by a train of pulses.

Iontophoretic application of the glutamate antagonist, glutamic acid diethyl ester (GDEE; 40-120 nA) blocked the excitatory responses of 5 of 10 (50%) accumbens neurones to hippocampal stimulation (Table 4).

FIGURE 8

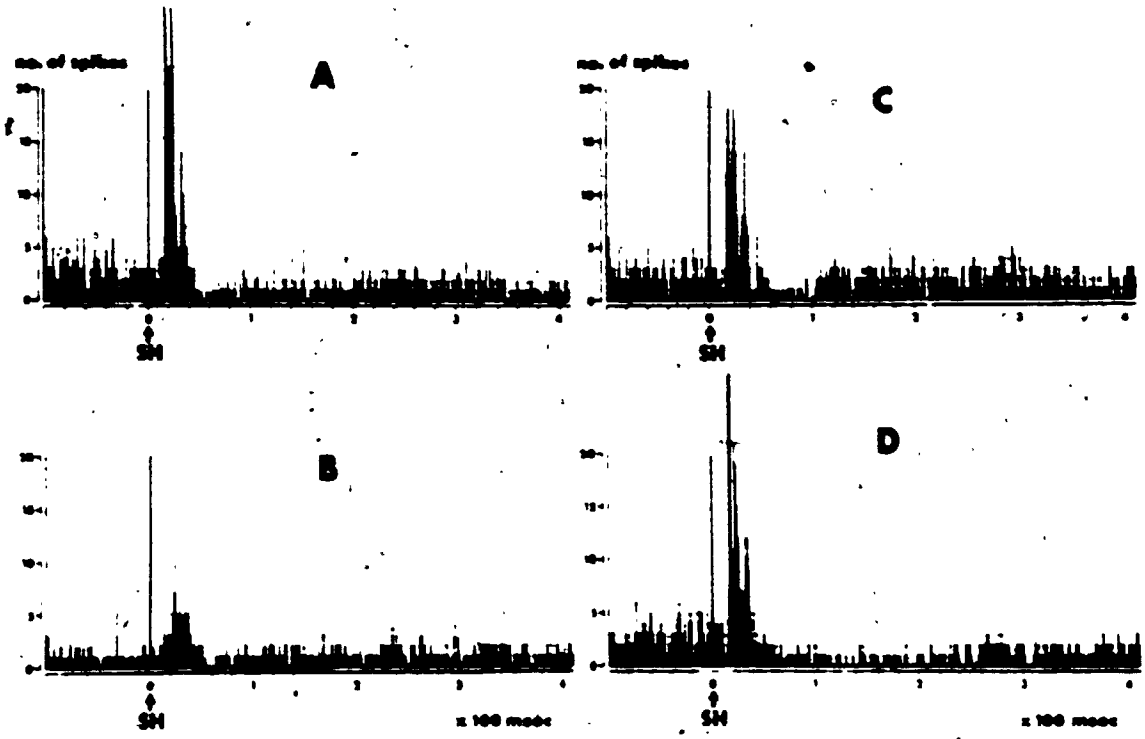
Peristimulus time histograms showing attenuation of the excitatory response of a spontaneously active accumbens neurone by iontophoretic application of dopamine, and its slow recovery.

A: Excitatory response of a spontaneously active accumbens neurone to hippocampal stimulation (400uA, 0.15 ms duration at 0.5 Hz) during the iontophoretic application of Na^+ (20nA) as a control. The excitatory response did not differ from that obtained without Na^+ application.

B: Attenuation of the excitatory response when +20nA dopamine was applied iontophoretically to the accumbens neurone. Note that dopamine selectively attenuated the hippocampal evoked excitatory response but leaving the baseline firing rate of the accumbens neurone with little changes.

C: 7 mins after the application of dopamine was terminated, the excitatory response of this accumbens neurone to hippocampal stimulation had not recovered to the control level as in (A).

D: 17 mins after the termination of dopamine application the excitatory response of this accumbens neurone to hippocampal stimulation had recovered fully.


A
B
C
D
SH
SH
SH
SH
x 100 msec
x 100 msec

1.4 Effects of 6-Hydroxydopamine and Haloperidol Treatment on the Interaction of Hippocampal Stimulation and VTA Conditioning Stimulation.

In 12 rats, 6-hydroxydopamine (6-OHDA) was injected unilaterally into the VTA 2 days (n=7) or 7-9 days (n=5) before the recording experiment in order to damage the mesolimbic dopamine neurones.

In a series of 25 silent accumbens neurones activated by hippocampal stimulation, recorded from animals treated 2 days previously with 6-OHDA, there was no attenuation by VTA conditioning stimulation in 19(76%) of these neurones. When compared to the number of silent neurones whose excitation by hippocampal stimulation was attenuated by VTA conditioning stimulation in the untreated animals there was a statistically significant difference (X^2=27.8, $p<0.001$, Table 4). In a series of 18 spontaneously active accumbens neurones in the animals treated 2 days previously with 6-OHDA, there was no attenuation by VTA conditioning stimulation of 17 (94%) of those neurones. When compared to the number of spontaneously active neurones whose excitation by hippocampal stimulation was attenuated by VTA stimulation in the untreated animals there was a statistically significant difference (X^2 = 26.9, $p<0.001$; Table 4). Single pulse stimulation of the VTA produced both excitatory and inhibitory responses of spontaneously active accumbens neurones of 6-OHDA-treated animals, although there was no

attenuation of the excitatory responses of the accumbens neurones to hippocampal stimulation.

Eight silent accumbens neurones in 5 rats treated 7-9 days previously with 6-OHDA, were activated by single pulse stimulation of the hippocampus. Conditioning VTA stimulation did not reduce the activation of any of these accumbens neurones. However the iontophoretic application of dopamine (15-40 nA) markedly reduced the activation of these 8 accumbens neurones to hippocampal stimulation. The results for one of these neurones are shown in Fig. 9.

In a separate series of 8 rats, haloperidol (0.5mg/kg, i.p.) was injected an hour before the recording session in order to block the dopamine receptors in the nucleus accumbens. In a series of 41 accumbens neurones recorded in the accumbens, the excitatory responses of 24 (59%) of them to hippocampal stimulation were unaffected by VTA conditioning stimulation and 17 (41%) were attenuated by VTA conditioning stimulation ($X^2=22$, $p<0.001$). Also, in a series of 18 spontaneously active accumbens neurones recorded from haloperidol-treated rats, the excitatory responses of 12 (67%) of the neurones were not attenuated by VTA conditioning stimulation and 6 (33%) were attenuated. When compared to the number of the silent and spontaneously active accumbens neurones whose excitation by hippocampal stimulation was attenuated by VTA conditioning stimulation in the untreated animals there was a statistically

FIGURE 9

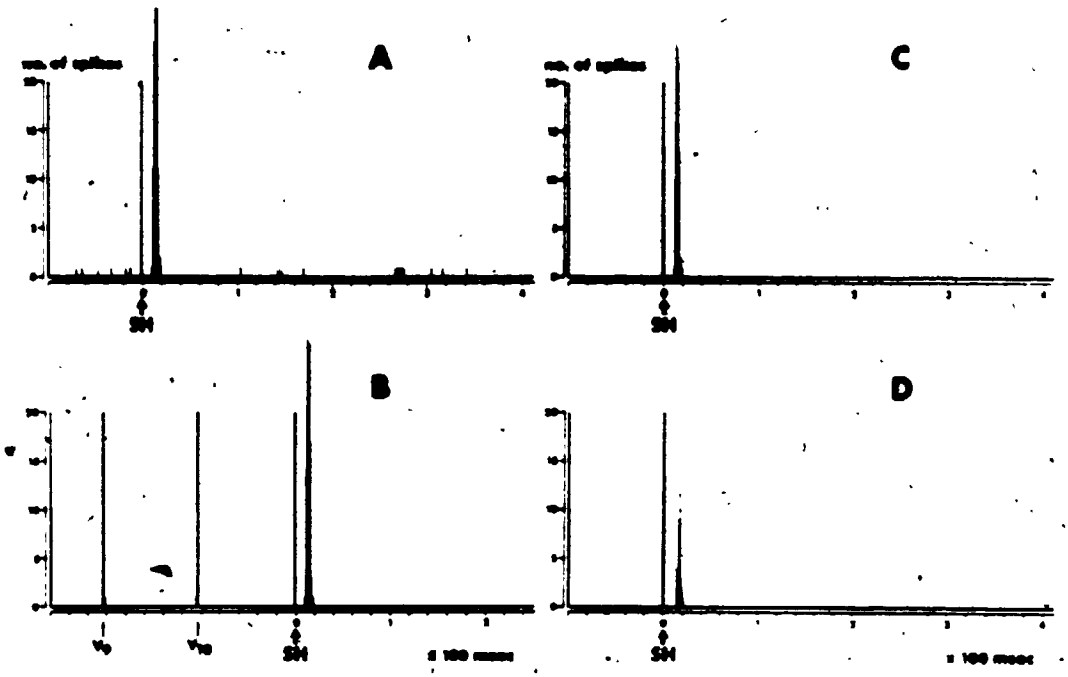
Peristimulus time histograms showing the absence of attenuation of the excitatory responses of an accumbens neurone to hippocampal stimulation by conditioning stimulation of VTA which was pretreated with 6-OHDA 9 days prior to the recording session. The same excitatory response was attenuated following the iontophoretic application of dopamine. All hisotograms were compiled from 150 sweeps.

A: Excitatory response of a silent accumbens neurone to single-pulse stimulation of the hippocampus (800uA, 0.15ms at 0.5 Hz).

B: No attenuation of the excitatory response of this accumbens neurone to hippocampal stimulation after interaction with the stimulation of the 6-OHDA treated VTA by trains of pulses (700uA, 0.15ms at 10 Hz). V9 and V10 represent the last two of 10 pulses delivered to the VTA before each single-pulse stimulation of the hippocampus (SH).

C: The excitatory response of this accumbens neurone did not differ from that of the control (see A) when Na^+ (40nA) was applied iontophoretically.

D: Marked attenuation of the excitatory response of this neurone when dopamine (15 nA) was applied iontophoretically.


A
C
B
D
SM
SM
SM
SM

significant difference (χ^2 = 14.1, $p<0.001$)(Table 4). In another series of 4 rats, trifluoperizine, iontophoretically applied (15-40 nA) onto 8 out of of 10 accumbens neurones studied, blocked the attenuation (by 55-97%) of the excitatory response to hippocampal stimulation following conditioning stimulation of the VTA.

In summary, this series of experiments has shown that the majority of accumbens neurones was excited by hippocampal stimulation. Conditioning stimulation of the VTA and iontophoretic application of dopamine attenuated these excitatory responses in the same accumbens neurone. Furthermore, this attenuating effect in a number of accumbens neurones was reduced by: 1) 6-hydroxydopamine lesion of the VTA prior to a recording session; 2) intraperitoneal injection of haloperidol, a dopamine receptor antagonist; 3) iontophoretic application of trifluoperazine, another dopamine antagonist, to accumbens neurones.

2.0 Antidromic Responses of Hippocampal-Accumbens Neurones.

2.1 Antidromic Responses of Ventral Subiculum Neurones to Medial Accumbens Stimulation and the Changes of Their Excitability by Conditioning Stimulation of the VTA.

Single pulse stimulation (0.15-0.2 ms pulse width at 0.5 Hz) of the medial accumbens elicited short latency antidromic action potentials in 283 hippocampal neurones in 78 rats studied. The onset latencies of 80% of them fell

within the range of 10-12 ms as shown by the single peak of the unimodal distribution of the onset latencies (Fig. 10D). Since all the antidromic responses exhibited a typical triphasic wave form with the duration of the action potential of at least 1 ms (Fig. 10A-C), they are considered extracellular recordings from the cell bodies of HIPP-ACC neurones. Before each experimental treatment performed on the identified HIPP-ACC neurones a baseline firing index of 35-40 was first established by means of threshold stimulation of the accumbens to evoke 6-8 antidromic responses in 5-10 sets of 20 stimulation trials (see Methods). There was some fluctuation of baseline firing index. Hence, during the control periodic fine adjustment of the accumbens stimulation by changing the pulse duration at 0.01ms step up to a maximum of 0.25ms was performed in order to ensure a stable baseline firing index. Neurones which did not maintain a stable baseline firing index of 30-40 in a minimum of 6 consecutive sets, or whose firing index fluctuated more than 50 % of the initial value, were excluded (n=35).

Conditioning pulses (200-800uA, 5-10 trains, 10 pulses per train delivered at 0.6 Hz), but not single pulses, presented to the VTA, 40-80 ms before each single-pulse stimulation of the accumbens, produced an abrupt increase in firing index which exceeded by two-fold the control values

FIGURE 10

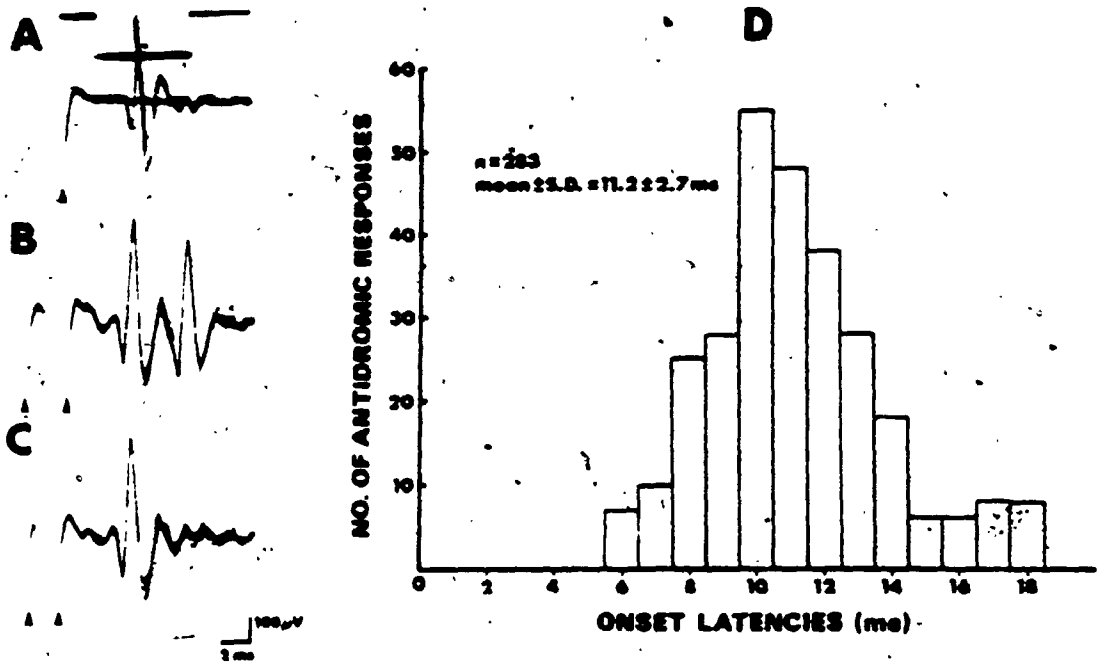
Antidromic responses of a HIPP-ACC neurone and the distribution of the onset latencies of these responses.

A: Antidromic responses of a ventral subiculum neurone of the hippocampus to medial accumbens stimulation(50uA, 0.2ms duration,0.6 Hz, 5 sweeps) which met the criteria of constant latency, all-or-nothing responses at threshold stimulation. The square pulse in the upper channel of the oscilloscope tracing indicates the pulse of the sampling time gate. The occurrance of the antidromic responses fell within the gated interval of the sampling time pulse.

B: Another criterion was high frequency following as tested by paired-pulse suprathreshold stimulation. In this neurone, the delay interval of the two pulses was 2.6ms;

C: In the same neurone, antidromic responses followed up to 500 Hz since the second pulse failed to evoke an antidromic response when the delay interval between the two pulses was shortened to 2.1ms (Calibration:2ms, 100uV).

D: Histogram showing the onset latencies of the antidromic responses with the majority of the responses occurring typically at 10-12ms.


A
B
C
D
n = 283
mean ± S.D. = 11.2 ± 2.7 ms
NO. OF ANTIDROMIC RESPONSES
ONSET LATENCIES (ms)
0
2
4
6
8
10
12
14
16
18
10
20
30
40
50
60

in 78 of 110 neurones tested [$F(29,254)=5.13$, $p<0.001$] (Fig. 11, Table 5). However, if the accumbens stimulation was adjusted so that the baseline firing index was near zero, conditioning VTA stimulation produced little or no change in this baseline firing index.

The enhancement of the firing index continued for several mins (Fig. 11) and was of greater magnitude (Fig. 12) and of longer duration with higher intensity VTA stimulation (compare Fig. 14A, 200uA with Fig. 14B, 400uA). In 21 neurones studied, recovery occurred in 8-10 min (Fig. 11) and for another 25 neurones, recovery did not occur during the period of recording, up to 3 hr.

2.2 Iontophoretic Application of Dopamine to the Axonal Terminals of Hippocampal-Accumbens Neurones.

The firing index of 36 of 70 (51%) HIPP-ACC neurones was also enhanced by the iontophoretic application of dopamine (60-160nA, for 30-90 secs) to their axonal terminal regions in the accumbens. For 12 of 33 (36%) of these neurones, there was an enhanced firing index with iontophoretically applied dopamine as well as with conditioning VTA stimulation (Fig. 13A). Although both VTA stimulation and dopamine application produced a similar increase in firing index, the onset of the dopamine effect was more gradual than that produced by conditioning VTA stimulation. Usually, the onset of the effects of iontophoretically applied dopamine took 30-100 secs to develop. In addition,

FIGURE 11

Effects of conditioning VTA stimulation on the post-stimulation firing index of HIPP-ACC neurones. Baseline firing index was monitored for 10 min before conditioning VTA stimulation (500uA, 5 trains of 10 Hz pulses, n=21) delivered at time shown by arrow. A 150 % increase in firing index occurred during (filled circle, one-way ANOVA: $F(29,254)=5.13$, $p<0.001$), and persisted after, VTA stimulation. Recovery to baseline level occurred at 8 mins after termination of VTA stimulation. All values are expressed in mean±S.E.M.

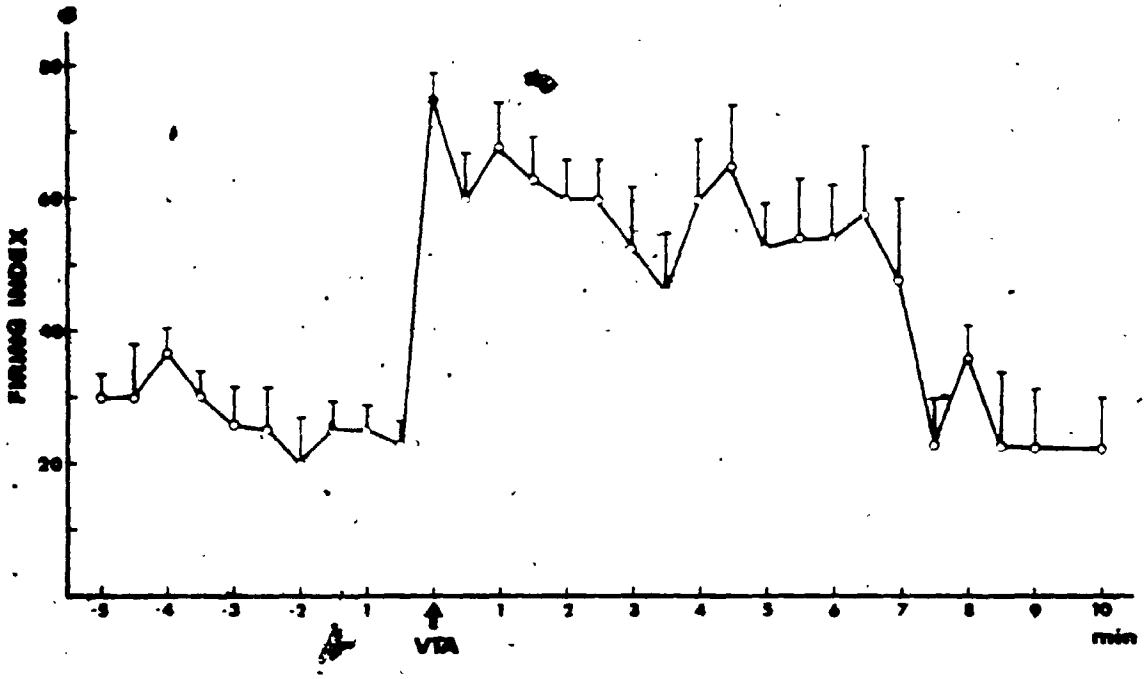

FIRING INDEX
60
40
20
-5
-4
-3
-2
-1
1
2
3
4
5
6
7
8
9
10
min
VTA

FIGURE 12

Firing index of HIPP-ACC neurones as the intensity of VTA stimulation was increased.

Open bars: mean firing index of the last five consecutive sets of test trials(each firing index was tabulated from antidromic responses evoked from 20 presentations of accumbens stimulation which made up a test set) prior to conditing VTA stimulation.

Filled bars: mean firing index determined from 5 sets of post-stimulation trials following conditioning VTA stimulation(10 trains of 10 Hz pulses pulses delivered at 0.6 Hz per train).Current intensity is indicated in the abscissa. Numbers at the bottom of each histogram indicate the number of neurones studied in each group. Asterisks indicate $p < 0.001$ following paired 't'-test which compared the firing index before and after conditioning VTA stimulation.

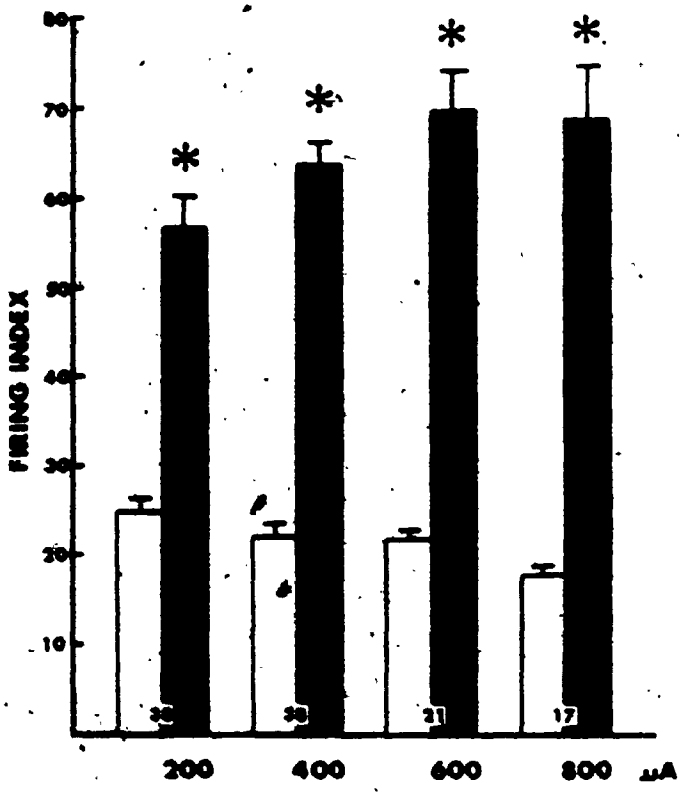
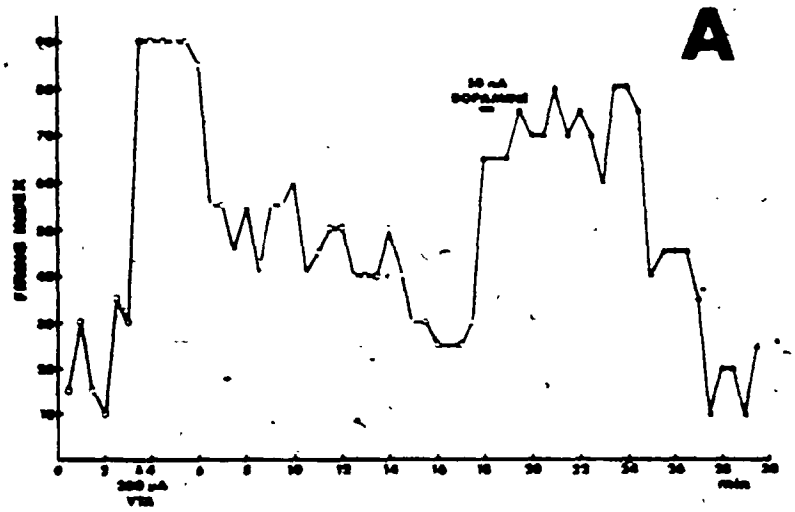

FIRING INDEX
70
60
50
40
30
20
10
*
*
*
*
30
30
21
17
200
400
600
800
μA

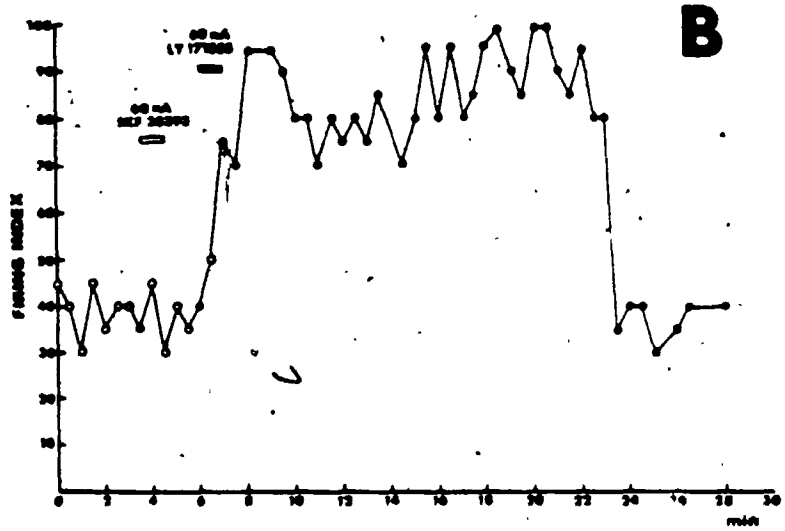
FIGURE 13

Effects of conditioning VTA stimulation, iontophoretic application of dopamine, its D-1 agonist SKF38393, and its D-2 agonist LY171555 on the firing index of two HIPP-ACC neurones.

A: Conditioning VTA stimulation (200uA, 5 trains of 10 Hz pulses) elicited an increase in firing index which lasted for 14 mins (closed circles). Subsequent iontophoretic application of dopamine (50nA) also produced a similar prolonged increase in the firing index of the same neurone (closed triangle).

B: In another HIPP-ACC neurone, iontophoretic application of the D-1 agonist SKF38393 (60 nA) did not change the baseline firing index, whereas iontophoretic application of LY171555(60nA) a dopamine D-2 agonist ,produced a four fold increase in the firing index for more than 12 min (closed circles).


A
min


B
min

iontophoretic application of potassium, a depolarizing agent, to the axonal terminal regions of 3 HIPP-ACC neurones produced similar increase in firing index. In cases for which no changes in firing index were observed following either VTA stimulation or dopamine application, it is likely that the accumbens stimulating electrode was positioned on the preterminal regions of HIPP-ACC axons where dopamine receptors are absent and hence, the effects of dopamine receptor activation could not be detected.

2.3 Comparison of Selective D-1 and D-2 Antagonists on the Enhanced Firing Index Produced By Conditioning VTA Stimulation.

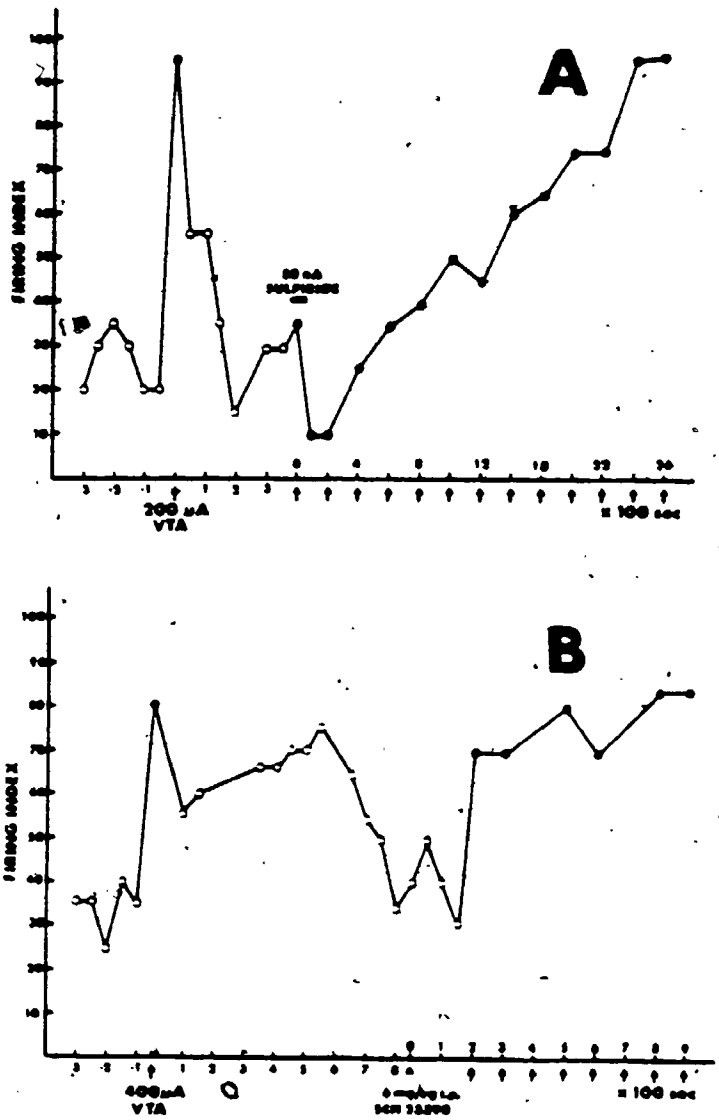
The enhanced firing index from conditioning VTA stimulation was blocked by sulpiride, a dopamine D-2 antagonist, when administered iontophoretically (20-80nA, 9/11 neurones)(Fig. 14A) or by intraperitoneal injection (20mg/kg, 5/7 neurones). The sulpiride treatment reduced the enhanced firing index of the same neuronal terminals that were attenuated by conditioning VTA stimulation or iontophoretic application of dopamine (iontophoretic application of sulpiride: 2 of the 11 neurones studied; intraperitoneal injection of sulpiride: 3 of the 7 neurones studied). When the conditioning VTA stimulation (5 trains of 10 Hz pulses) was repeated at intervals of 200sec the firing index increased gradually back to the pre-drug control level (Fig. 14 A).

FIGURE 14

Effects of iontophoretic application of sulpiride, a dopamine D-2 antagonist, and intraperitoneal injection of SCH 23390, a dopamine D1 antagonist, on the increased firing index of HIPP-ACC neurones produced by conditioning VTA stimulation.

A: Conditioning stimulation of VTA (200uA, 5 trains of 10 Hz pulses as indicated by the arrow) produced a four fold increase in firing index of this neurone. Following recovery to baseline, the increase in firing index produced by the same VTA stimulation was blocked by iontophoretic application of sulpiride(80nA). Conditioning VTA stimulation at 200 sec interval (arrows) slowly brought the enhanced firing index (filled circles) back to pre-drug level.

B: In another neurone, conditioning VTA stimulation (400uA, 5 trains of 10 Hz pulses as indicated by the arrow) produced over a two-fold increase in firing index during and after the stimulation. The enhanced firing index lasted for 800 secs. Intraperitoneal injection of SCH 23390 (6mg/kg) did not block the enhanced firing index produced by conditioning VTA stimulation. Conditioning VTA stimulation delivered at 200 sec interval (arrows) still enhanced the firing index.


A
B
VTA
VTA

No change in the enhanced firing index was produced by conditioning VTA stimulation in any of the 7 neurones tested when SCH23390, a selective central dopamine D-1 antagonist was injected intraperitoneally (6-10 mg/kg, Fig. 14B).

2.4 Comparison of Selective D-1 and D-2 Agonists on The Firing Index of Hippocampal-Accumbens Neurones.

In order to permit detection of increases or decreases of the firing index with the iontophoretic application of the D-1 and D-2 agonists stimulating current delivered to the accumbens was first adjusted to produce a baseline firing index of 40-50. Direct iontophoretic application of LY171555 (Quinpirole hydrochloride, 60-160nA), a selective dopamine D-2 agonist, onto axonal terminals of HIPP-ACC neurones, enhanced the firing index in 17 of 31 neurones (55%) tested (Fig. 13B) and in 6 of 17 neurones (35%) the firing index was increased by both the iontophoretic application of DA or LY171555 (Table 5). The onset of responses and the prolonged duration of the enhanced firing index produced by LY171555 or dopamine were similar. However, iontophoretic application of SKF38393, a dopamine D-1 agonist did not change the firing index at current range of 40-120 nA. At higher iontophoretic current (140-160nA), this D-1 agonist had a tendency to suppress baseline firing index of the HIPP-ACC neurones. A differential response to SKF38393 (no change) and LY171555 (enhanced) was observed in

Table 5 Number of hippocampal neurones antidromically activated by accumbens stimulation and tested with conditioning VTA stimulation, or with iontophoretic application of DA, LY171555 or SKF38393 onto the terminal region of HIPP-ACC neurones.

	No. of antidromic responses tested with						
	Conditioning VTA stimulation (200-800uA)	Iontophoretic application of DA (40-160 nA)	Responded to both VTA stimulation & DA application	Iontophoretic application of LY171555	Responded to both DA and LY171555	Responded to LY171555, but not to SKF38393	Total tested
1) Enhanced firing index	78/110(71%)	36/70(51%)	12/33(36%)	33/69(48%)	6/17(35%)	21/35(60%)	212
no response	32/110(29%)	35/70(49%)	-	36/69(52%)	-	-	
2) Enhanced firing index after ibotenic acid lesion of accumbens	36/54 (67%)	10/17(59%)	5/15(33%)	9/15(60%)	-	-	71
no response	18/54 (33%)	7/17(41%)	-	6/15(40%)	-	-	

* Only neurones which showed changes in firing index by 100 % or above are included in this table. (see legends of Fig.1, METHODS section).

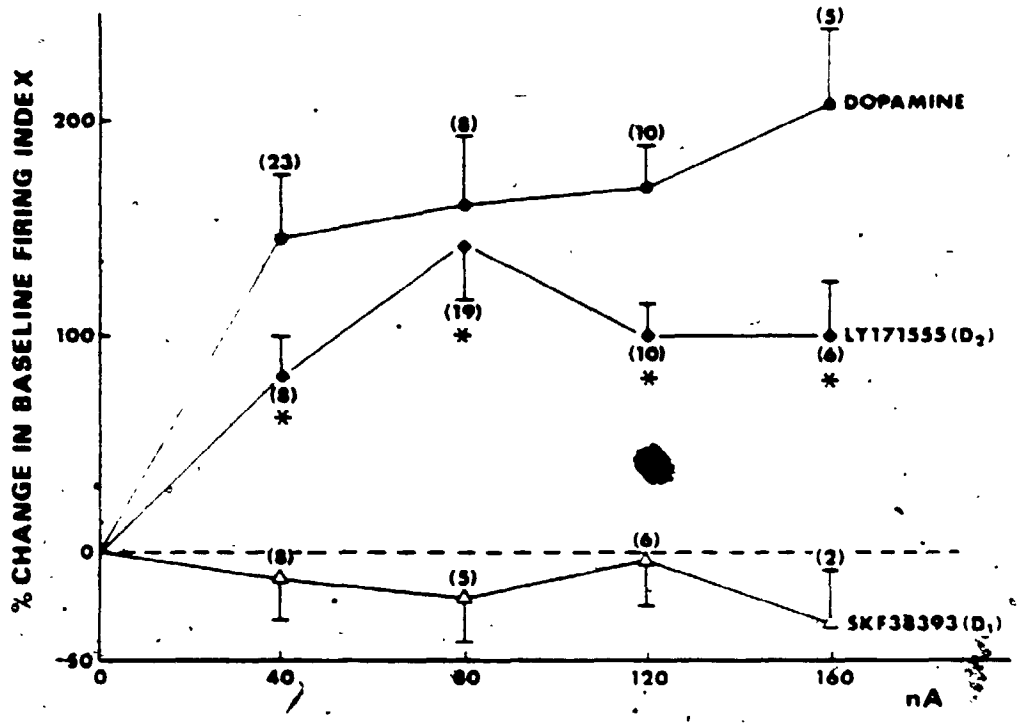
21 of 35 neurones (60%) tested (Fig. 13B). The percentage change in firing index is shown in Fig. 15. The dopamine effect was greater than that produced by LY171555 and this may reflect a lower baseline firing index used to obtain a better resolution in the responses for the dopamine effects, i.e., primarily enhancement in firing index.

2.5 Effects of Ibotenic Acid Lesions of the Medial Accumbens on the Firing Index Produced by Conditioning VTA Stimulation, Iontophoretic Application of Dopamine, or its D-2 Agonist, LY171555.

Ibotenic acid lesions of the accumbens did not change the onset and duration of the enhanced firing index due to conditioning VTA stimulation in 36 of 54 neurones(67%) tested (Table 5). The enhanced firing index produced by the iontophoretic application of dopamine in 59%(10/17), or of LY171555 in 60%(9/15) of neurones was also not affected. Five of 15 (33%)neurones responded to both conditioning VTA stimulation and iontophoretic application of dopamine. The proportion of neurones showing an enhanced firing index by VTA stimulation or dopamine application in the ibotenate lesioned rats was not significantly different from those neurones recorded from normal rats (Chi Square (X^2)=0.63, p>0.1). Histological examination of brain sections stained with thionine showed a loss of neuronal cell bodies and the presence of extensive gliosis confined to the dorsal medial part of the nucleus accumbens.

FIGURE 15

Changes of baseline firing index of HIPP-ACC neurones by dopamine, LY171555 and SKF38393 delivered by different iontophoretic currents. The percentage change in firing index was calculated by comparing the mean value determined from the last six stable baseline firing indices with the mean value of six firing indices obtained following iontophoretic application of the dopamine agonists. All values are expressed as mean $\pm$ S.E.M., with the S.E.M. drawn in one direction only for clarity. The numbers in brackets represent the number of neurones tested. For those neurones whose baseline firing index were not altered by SKF38393 but instead, selectively enhanced by LY171555, their changes in firing index at each iontophoretic current were compared using a paired-t test with * indicating $p<0.001$.


% CHANGE IN BASELINE FIRING INDEX
200
100
0
-50
0
40
80
120
160
nA
DOPAMINE
LY171555 (D2)
SKF38393 (D1)
(23)
(8)
(10)
(5)
(8)
(19)
(10)
(6)
(8)
(5)
(6)
(2)
*

In summary, antidromic responses of ventral subicular neurones of the hippocampus were evoked by stimulation of the medial accumbens. The baseline terminal excitability of some hippocampal neurones, established by threshold stimulation of the accumbens, was markedly enhanced by conditioning stimulation of the VTA, the origin of the mesolimbic dopaminergic neurones. Iontophoretic application of sulpiride, a selective dopamine D-2 antagonist, presumably onto the HIPP-ACC neuronal terminal regions, attenuated the increased terminal excitability of these neurones produced by conditioning VTA stimulation whereas intraperitoneal injection of SCH23390, a selective D-1 antagonist, failed to attenuate this effect. Iontophoretic application of dopamine or its selective D-2 agonist, LY171555, as well as potassium, on the terminal regions of the HIPP-ACC neurones mimicked the prolonged enhancement of the terminal excitability produced by VTA stimulation whereas SKF38393, a D-1 agonist, had no effect. Following ibotenate lesion of the accumbens, the effects of VTA stimulation, dopamine and LY171555 application on the enhanced terminal excitability of the hippocampal-accumbens neurones still persisted.

3.0 Electrophysiology of Output Neurones of the Nucleus Accumbens to Ventral and Subpallidal regions.

3.1 Electrophysiological Responses of Neurones in the Nucleus Accumbens to Hippocampal Stimulation and Their Antidromic Responses to Pallidal Stimulation.

Extracellular single-unit recordings were made from 185 neurones histologically verified to be located in the medial nucleus accumbens (Fig. 16) of 30 rats. Single pulse stimulation of the ventral subiculum of the hippocampus (200-800 uA, 0.2ms, 0.6-1.0 Hz) excited the accumbens neurones which were otherwise silent. Hippocampal stimulation elicited a burst of 3-4 spikes as indicated by multiple peaks in the peristimulus time histogram in Fig. 17. The mean onset latencies of these orthodromic excitatory responses was 10 ms (range 9-13ms). The accumbens neurones activated by hippocampal stimulation were investigated further for their antidromic responses to stimulation of the subcommissural ventral pallidum or the sublenticular subpallidal region.

Fifty-five (30%) of the 185 medial accumbens neurones, synaptically activated by hippocampal stimulation, also responded antidromically to single-pulse stimulation of VP (sites shown in Fig. 18). A typical antidromic response is shown in Fig. 17 (inset) and the criteria for antidromic activation are illustrated in Fig. 19 A,B. With a suitable delay interval between hippocampal and VP stimulation, orthodromic excitatory responses of the same silent

FIGURE 16

Coronal sections of the rat brain showing the recording sites in the nucleus accumbens of neurones activated by stimulation of the ventral subiculum of the hippocampus. Filled circles (●) indicate locations of those neurones which were antidromically activated by stimulating subcommissural ventral pallidum or sublenticular subpallidal area. Open circles (○) indicate those neurones which show no response to stimulation of either pallidal sites. Open squares (□) represent sites where accumbens neurones showed no response to stimulation of both pallidal sites. The number on the right hand side of each section indicates distance in milimetres anterior to the bregma according to a standard stereotaxic atlas of the rat brain (Pellegrino et al.,1979). Abbreviations: ACC, nucleus accumbens; CC, corpus callosum; CPU, caudate-putamen; DBB, digonal band of Broca.

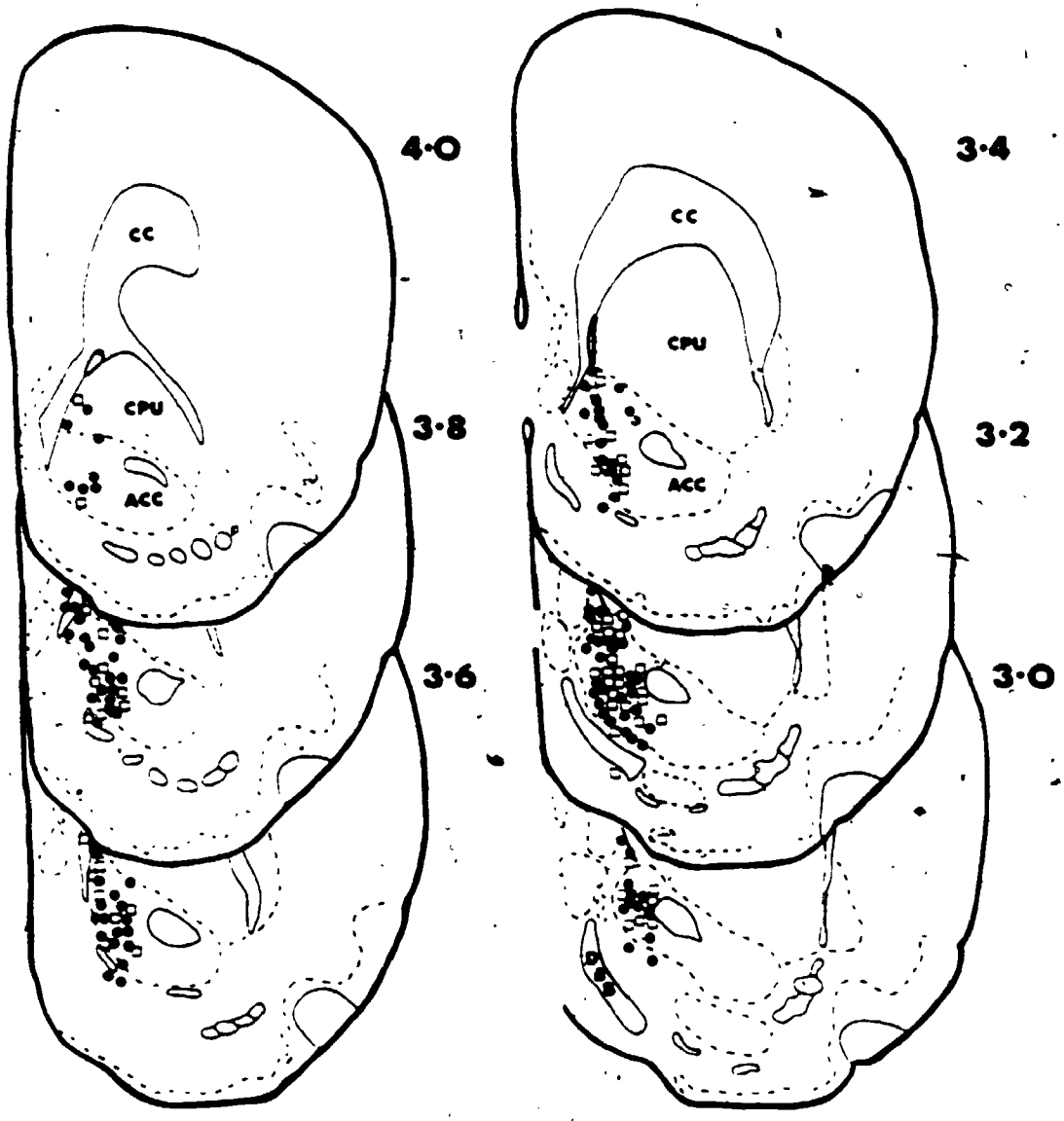

4·0
3·8
3·6
3·4
3·2
3·0
CC
CPU
ACC
CC
CPU
ACC

FIGURE 17

A peristimulus time histogram showing a typical response of an accumbens neurone to the stimulation of the ventral subiculum of the hippocampus at the time indicated by the arrow (SH). Current pulses of 500uA for 0.2 ms duration were delivered at 0.5 Hz and the histogram was compiled from 150 sweeps. The latency of this orthodromic excitatory response was 12 ms. Insert shows an antidromic response of this accumbens neurone to stimulation (1.2 mA, 0.2-ms duration) of the subcommissural ventral pallidum. The photographic record was of 10 sweeps taken from the oscilloscope. The arrow SVP indicates the time of stimulation. The onset latency of this antidromic response was 6 ms. Calibration: 100uV and 2 ms. Downward is positive.

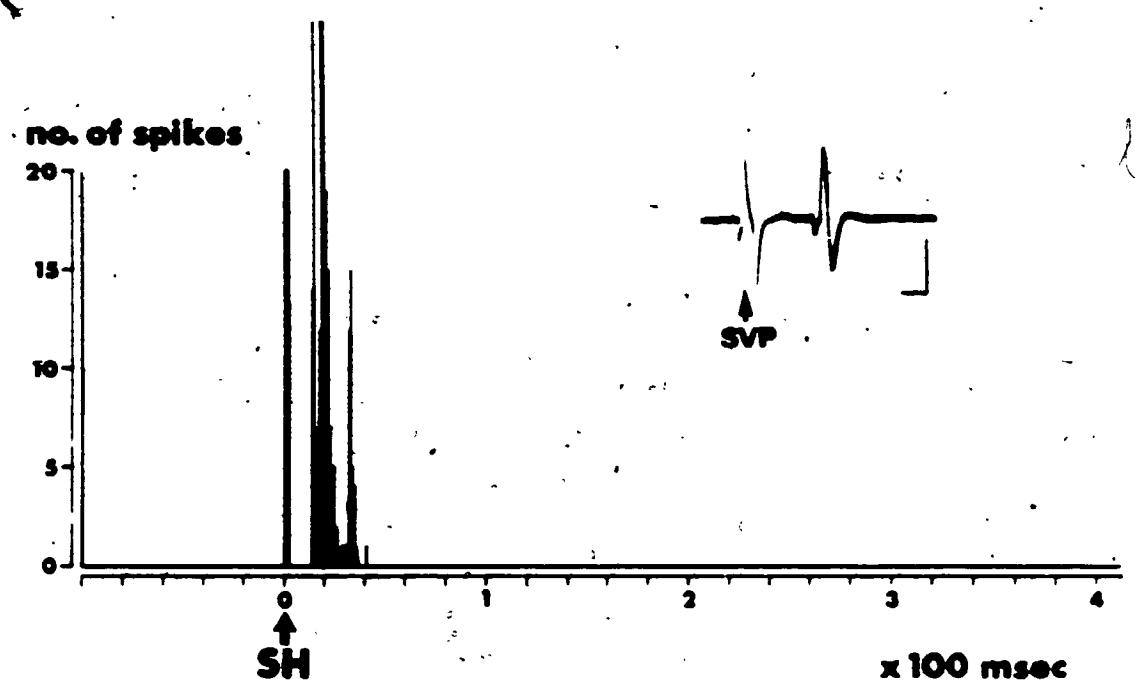

no. of spikes
20
15
10
5
0
0
1
2
3
4
SH
x 100 msec
SVP

FIGURE 18

Distribution of stimulation sites in the subcommissural ventral pallidum (upper section) and sublenticular subpallidal region (lower section) are shown in the drawings of transverse section of the rat brain. Stimulation sites where neurones recorded in the nucleus accumbens were antidromically activated are shown by filled triangle (▲). Stimulation in sites where neurones recorded in the accumbens did not respond antidromically were represented by inverted open triangle (▽). Abbreviations: AC, anterior commissure; CC, corpus callosum; CPU, caudate-putmen complex; GP; globus pallidus; IC, internal capsule; LH, lateral hypothalamus; LPO, lateral preoptic area; LS, lateral septum; SI, substantia innominata.

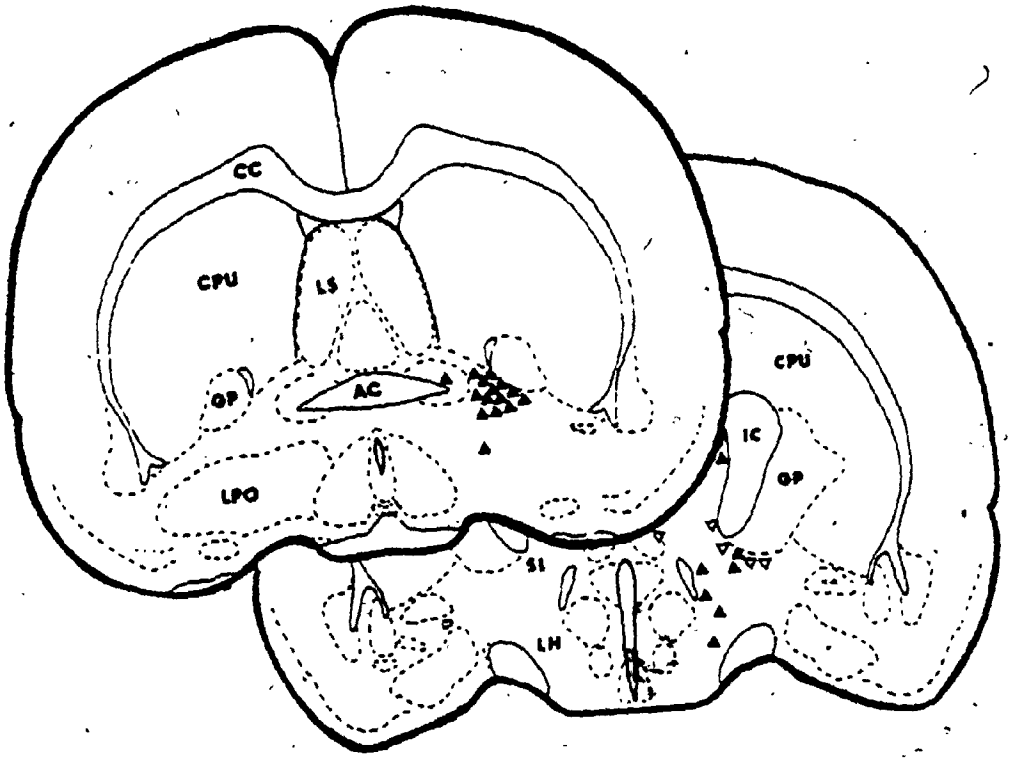

CC
CPU
LS
AC
OP
LPO
SI
LH
CPU
IC
OP

FIGURE 19

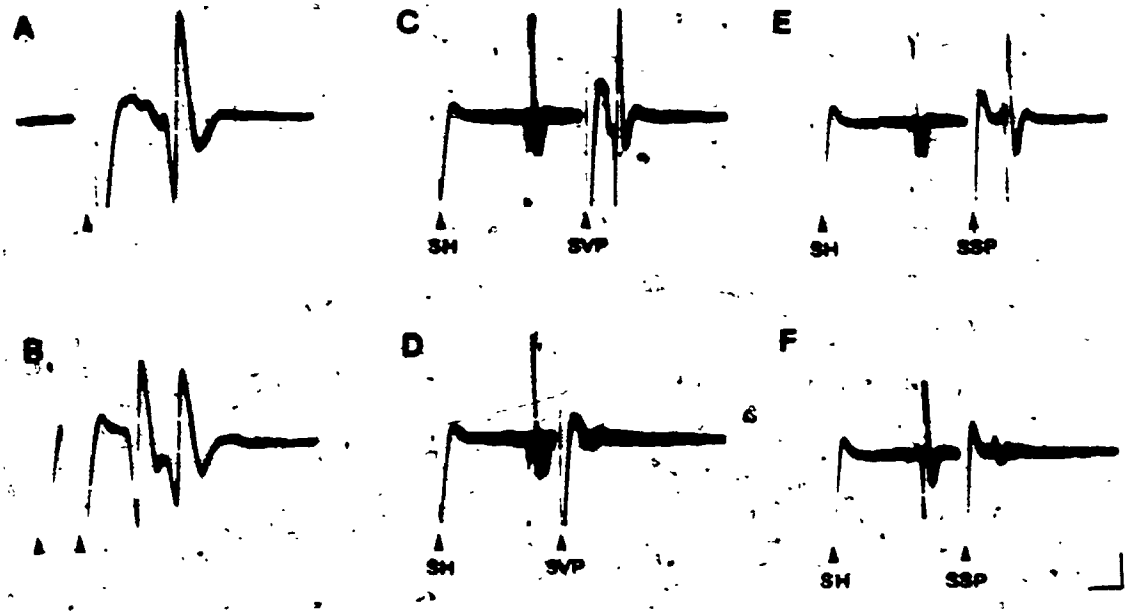
Microelectrode recordings made from accumbens neurones which were excited by hippocampal stimulation (SH) and antidromically activated by either VP or SP stimulation.

A: Constant onset latency of the antidromic responses to VP stimulation (SVP);

B: High frequency following of paired pulses delivered 1.5ms apart (corresponding to 666 Hz stimulation);

C andD: illustrate the response of the accumbens neurone when the delay interval between hippocampal and VP stimulation was shortened. When the orthodromic excitatory responses evoked by SH(note the jittery responses) fell within the critical delay period, these responses "collided" with the antidromic spikes elicited by VP stimulation.

E and F: Antidromic responses of the accumbens neurone to SP stimulation (SSP) "collided" with the synaptically evoked spikes from hippocampal stimulation stimulation (SH) when the delay interval between SH and SSP was shortened. All photographic records were compiled from 10 sweeps. Calibration: 100uV , 5ms. Downward is positive.


A
C
E
SH
SVP
SH
SSP
B
D
F
SH
SVP
SH
SSP

accumbens neurone to hippocampal stimulation "collided" with the antidromic spike elicited by VP stimulation (Fig. 20 C,D). The mean onset latency of the antidromic responses of these accumbens output neurones to VP stimulation was 7 ms (range, 4-10 ms) indicating they are also slow conducting neurones (mean conduction velocity 0.3m/s). There was no difference in the distribution of the antidromic responses recorded in the rostral (n=27; 15%) and caudal (n=28; 15 %) portion of the accumbens (Table 6).

In contrast, only 14 (7%) of the 185 accumbens neurones were activated antidromically by stimulation of the sublenticular subpallidal area. The antidromic stimulation sites shown in Fig. 18 were histologically verified to be located in the substantia innominata and part of the rostral lateral hypothalamus. When the interval between hippocampal and SP stimulation was shortened, the orthodromic excitatory responses of the silent accumbens neurones to hippocampal stimulation fell within the critical delay period and "collided" with the antidromic spike elicited from SP stimulation (Fig. 19E,F). The mean onset latency of these 14 antidromic responses to SP stimulation was 8.3 ms (range, 6-9 ms) indicating that they were recorded from slow-conducting neurones with a mean conduction velocity of 0.42m/s (Table 6). Three accumbens neurones were activated antidromically by either stimulation of VP or SP, raising the possibility that they represent collaterals of the same

Table 6

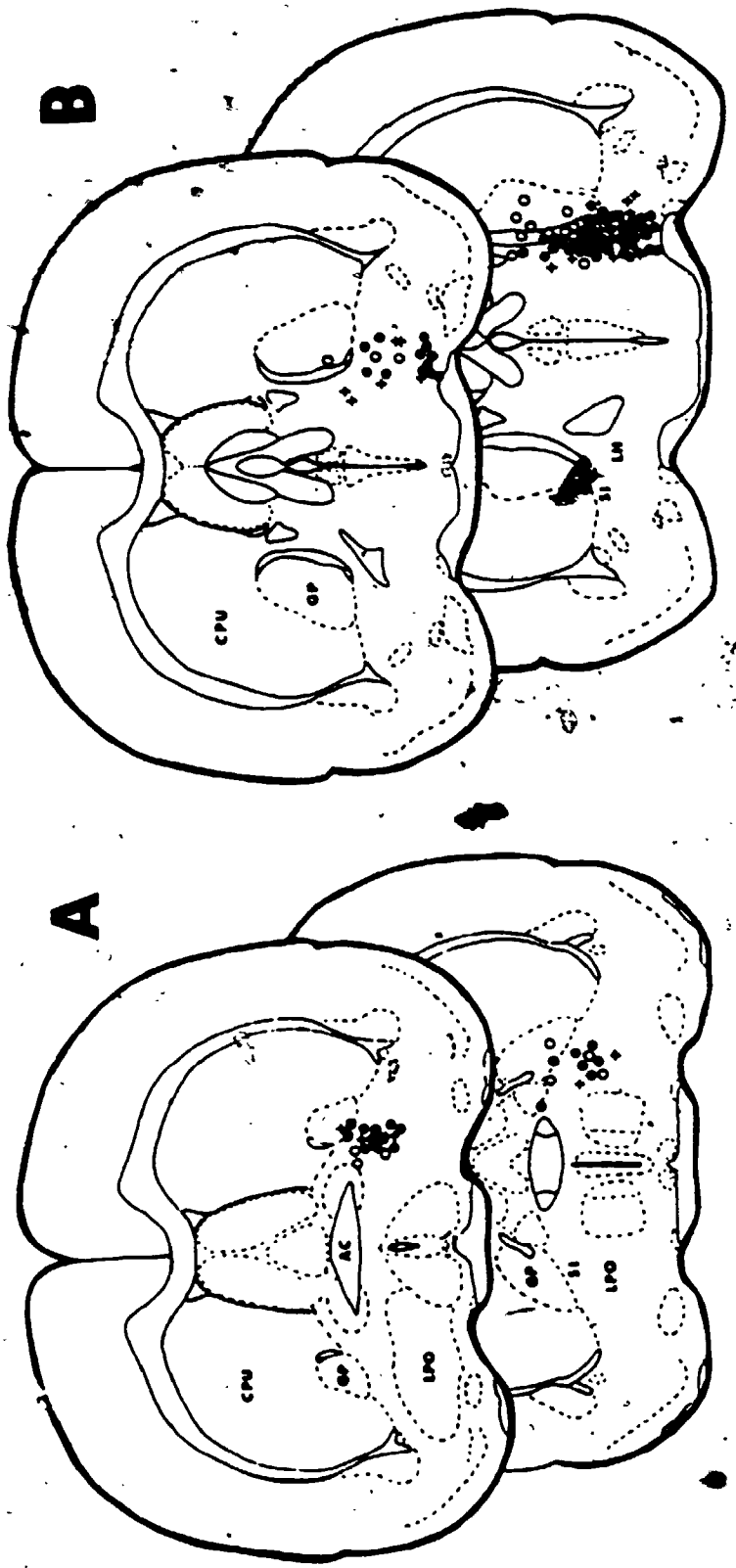
Antidromic and orthodromic responses of accumbens neurones to pallidal stimulation.

Responses of accumbens neurones to orthodromic hippocampal stimulation and also to stimulation of:	Medial nucleus accumbens neurones: Rostral [1]	Caudal [2]	Total (100%)	Onset latency (M.±S.E.) ms.
1. Subcommissural ventral pallidum				
antidromic :	27 (15%)	28 (15%).	55 (30%)	7 ± 0.4
orthodromic :	26 (14%)	35 (19%)	61 (33%)	6.2± 0.4
no response :	26 (14%)	43 (23%)	69 (37%)	
2. Sublenticular subpallidal area				
antidromic :	6 (3%)	8 (4%)	14 (7%)	8.3 ± 0.7
orthodromic :	1 (1%)	7 (4%)	8 (5%)	7.5 ± 0.6
no response :	71 (38%)	92 (50%)	163 (38%)	

1- The rostral aspect of the accumbens represents the region of the nucleus 4.0-3.5 mm anterior to the bregma.
2- The caudal aspect of the accumbens represents the region of the nucleus 3.4-3.0 mm anterior to the bregma.

FIGURE 20

Microelectrode recording sites in the subcommissural ventral pallidum (A) and in the sublenticular subpallidal regions (B) are shown on drawings of transverse sections of the rat brain. The sites where neurones were inhibited by single-pulse stimulation of the hippocampus were shown by filled circles (●). Sites where neurones were excited by single-pulse stimulation of hippocampus are shown by crosses (+). Sites where spontaneously active neurones did not respond to stimulation of hippocampus are shown by open circles (O). Abbreviations: AC, anterior commissure; CPU, caudate-putamen complex; GP, globus pallidus; LH, lateral hypothalamic area; LPO, lateral preoptic area; SI, substantia innominata.


B
A
CPU
GP
3
AC
LGN

accumbens output neurones which project to both VP and SP regions.

Chi-square analysis showed that there were significantly more accumbens neurones responding antidromically to VP than to SP stimulation (Chi-square(X^2)=24.3, $p<0.001$). With a similar analysis it was found that the proportion of neurones in the rostral and caudal accumbens activated antidromically by stimulation of VP or SP areas were not significantly different, (Table 6).

3.2 Responses of Neurones of the Subcommissural Ventral Pallidum to Hippocampal Stimulation and the Reduction of These Responses By Microinjection of Glutamate Antagonist Into the Nucleus Accumbens.

A total of 38 spontaneously active neurones were recorded from VP sites as shown in Fig. 20. The spontaneous discharge rate of neurones in this basal forebrain region varied from 10 to 35 spikes/s with a mean of 21 spikes/s (Table 7). Single-pulse stimulation (200-800uA, 0.15ms, 0.6 Hz) of the ventral subiculum of the hippocampus elicited inhibition in 21 (75%) of these VP neurones. The mean onset latencies of the inhibitory responses was 16.3 ms (range, 3-27 ms) with the majority of the inhibitory responses within the range of 10-20 ms. The mean duration of these inhibitory responses was 26 ms.

The inhibitory responses to hippocampal stimulation before and after microinjection of GDEE (10-20ug in 0.5-1.0

Table 7

Responses of neurones in the subcommissural ventral pallidum (VP) and sublenticular subpallidal regions (SP) to hippocampal stimualtion.

	VP		SP	
Types of responses	inhibition	excitation	inhibition	excitation
No. of such responses	21	7	55	12
Mean firing rate (sp/s)	20.8±2.3	mostly silent	21±2	mostly silent
Onset latency of responses (ms)	16.3±1.2	9.4±1.0	17±0.8	11.4±1.2
Duration of responses (ms)	26±4.4	8.6±0.8	30±2.8	12.9±2.0
No response	10		20	
Total no. of neurones sampled	38		87	
No. of responses blocked by micro-injection of GDEE into the nucleus accumbens	12/17	1/6	9/16	2/4

firing rate, latency and duration are expressed in mean±S.E.M.

ul saline) into the accumbens were compared in 17 spontaneously active VP neurones. A typical response identical to that illustrated for an SP neurone in Fig. 21. The overall percentage of inhibition of the mean firing rate of the VP neurones following hippocampal stimulation was significantly reduced ($t=22.7$, $p<0.001$) after intra-accumbens injection of GDEE (Fig. 21 and Table 8). In addition the inhibitory responses of 12 (75%) if these VP neurones were reduced by over 25 % 5 min after intra-accumbens injection of GDEE. Following GDEE injection into the accumbens there was no significant change in the baseline firing of these VP neurones. Complete recovery of the response occurred within 50 min after injection in all of these responding VP neurones. Control injections of GDEE into the caudate nucleus, medial septum or injection of saline into the accumbens, produced no observable effects on the inhibitory responses of VP neurones to hippocampal stimulation. Furthermore, the VP neurones which responded orthodromically to hippocampal stimulation were distributed in the same region of the subcommissural ventral pallidum, stimulation of which evoked antidromic responses in the accumbens (compare Fig. 18 and 20).

3.3 Responses of Neurones in the Sublenticular Subpallidal Area To Hippocampal Stimulation and the Reduction of These Responses By Microinjection of Glutamate Antagonist Into the Nucleus Accumbens.

The electrophysiological characteristics of neurones

FIGURE 21

Peristimulus time histograms showing inhibitory response of a neurone recorded in the sublenticular subpallidal region to hippocampal stimulation and the response being blocked by microinjection of GDEE, a glutamate antagonist, into the nucleus accumbens.

A: Peristimulus time histogram showing the inhibitory response of the SP neurone to hippocampal stimulation at 200uA, 0.2 ms duration.

B: Six minutes after the microinjection of GDEE (20ug/ul) into the nucleus accumbens, the inhibitory response of the same neurone was blocked by 74% compared to the response in (A).

C: The inhibitory response of this same neurone recovered 40 min after the termination of the GDEE injection. All histograms were compiled from 120 sweeps at 0.6 Hz and the bin width is 1 ms. SH denotes the time of stimulation of the hippocampus.

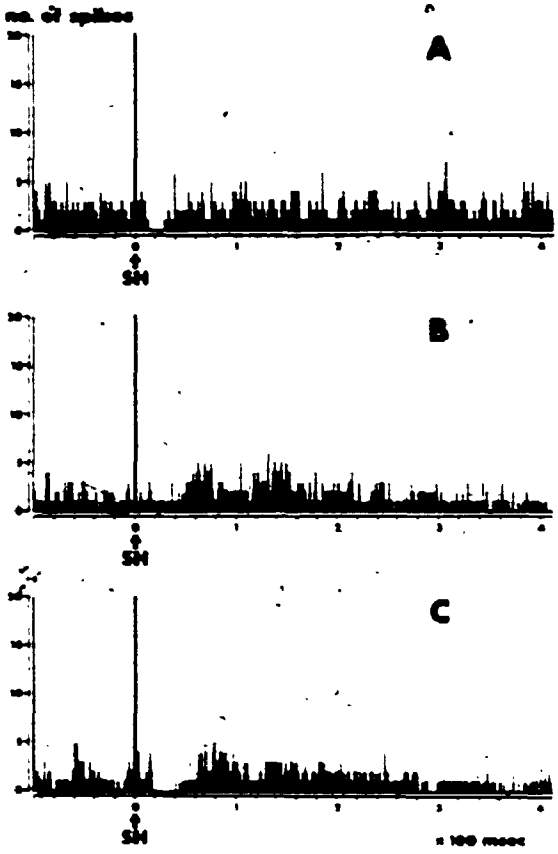

no. of spikes
A
SH
B
SH
C
SH
= 100 msec

Table 8 A comparison of the percentage of inhibition of mean firing rate of VP and SP neurones following hippocampal stimulation before(CONTROL) and after microinjection of GDEE into the medial accumbens.

	VP neurones		SP neurones	
	CONTROL	GDEE	CONTROL	GDEE
	(n=17)		(n=16)	
% inhibition of mean firing rate following hippocampal stimulation▽	79.8±2.9	45±4.2*	81.5±3	65±5.4*

▽ The mean firing rate of VP or SP neurones during an inhibitory response to hippocampal stimulation is expressed as a percentage of their baseline firing (CONTROL). Changes in this period after intra-accumbens GDEE injection was compared with the CONTROL.

Data are expressed as mean± S.E.M. *$p<0.001$ following paired 't' test.

recorded in the SP were very similar to those of the VP neurones. Single-pulse stimulation of the hippocampus inhibited 55 (82%) spontaneously active neurones recorded in the SP region. These SP neurones discharged at a mean firing rate of 21 spikes/s (Table 7). A broad distribution of the onset latencies of the inhibitory responses were observed with the mean onset at 17 ms (range, 6-24ms). All SP units recorded were histologically verified to be located in the substantia innominata and the lateral hypothalamic regions (Fig. 20B).

The inhibitory responses to hippocampal stimulation before and after the microinjection of GDEE (10-20 ug in 0.5-1.0 ul saline) were compared in 16 SP neurones (n=7 rats). The mean firing rate of the SP neurones following hippocampal stimulation was reduced significantly ($t=19$; $p<0.001$) after intra-accumbens injections of GDEE (Fig. 21, Table 8). In 9(56%) of these 16 SP neurones the inhibitory response to hippocampal stimulation was reduced reversibly by more than 25 % 5 min after the microinjection of GDEE (10-20 ug in 0.5-1.0 ul saline) into the medial accumbens (Table 8). Control injection produced no observable effect on the inhibitory responses of the SP neurones to hippocampal stimulation.

Excitatory responses of SP neurones to hippocampal stimulation were also recorded in 12 neurones, 6 of which

were spontaneously active. In these spontaneously active neurones the excitatory response was followed by a short period of inhibition. The mean onset latency of excitation was 11.4 ms and the mean duration was 13 ms. For 2 out of 4 excitatory responses studied, microinjection of GDEE into the accumbens reduced the response by over 25 % (Table 7).

3.4 Responses of Accumbens Neurones Synaptically Activated by Ventral Pallidum or Subpallidal Stimulation.

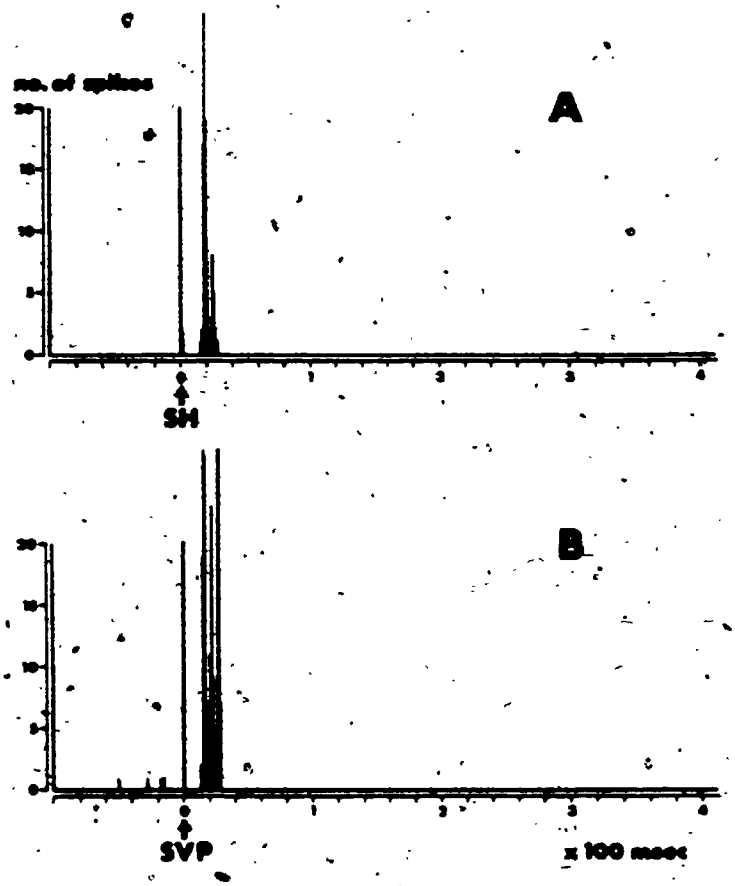
Sixty-one of 185 (33%) accumbens neurones synaptically activated by hippocampal stimulation were activated synaptically by stimulation of the subcommissural ventral pallidum. A typical response of these neurones is illustrated in Fig. 22. Twenty-six (14%) accumbens neurones synaptically activated by stimulation of the VP were located in rostral accumbens and 35 (19%) were in the caudal accumbens. The mean onset latency of these excitatory responses was 6.2 ms (Table 6). Eight (7%) accumbens neurones were also synaptically activated by stimulation of the sublenticular subpallidal area. One(1%) of these neurones was located in the rostral accumbens and 7 (4 %) were located caudally. The mean onset latency of the orthodromic responses of these accumbens neurones to subpallidal stimulation was 7.5 ms. Chi-square analysis indicated that there were significantly (X^2=49, $p<0.001$) more accumbens neurones synaptically activated by VP than by SP stimulation.

FIGURE 22

Peristimulus time histograms of typical responses of an accumbens neurone to hippocampal stimulation (SH) shown in (A) and to subcommissural ventral pallidal stimulation (SVP) shown in (B). Both histograms were compiled from 150 sweeps at 1 Hz.

A: Current pulses of 350 uA of 0.2ms duration were delivered to the ventral subiculum of the hippocampus. The onset latency of the excitation was 13 ms and the duration was 15 ms.

B: Current pulses of 900uA were delivered to the subcommissural ventral pallidal region. The onset latency of excitatory was 9 ms and the duration was 17 ms.


no. of spikes
A
SH
B
SVP
x 100 msec

In summary, this series of experiments has shown that neurones in the nucleus accumbens, synaptically activated by hippocampal stimulation, were activated antidromically by stimulation of the VP and SP areas. Over four times as many of these accumbens neurones responded antidromically to VP than to SP stimulation. Most of spontaneously active neurones in both the VP and SP areas were inhibited by hippocampal stimulation. When GDEE, a glutamate antagonist was injected into the accumbens, this inhibitory response was reduced significantly.

4.0 Electrophysiological Recordings of the Subpallidal Neurones.

4.1 Orthodromic Responses of Subpallidal Neurones to Hippocampal Stimulation and Their Antidromic Responses to PPN Stimulation.

Extracellular recordings were obtained from a total of 309 neurones in the sublenticular subpallidal area of 44 rats. Two hundred and twenty nine of these SP neurones were activated antidromically by stimulation of the medial PPN and the adjacent lateral portion of the central gray (200-800uA, 0.15 ms duration at 1.0 Hz)(Fig.23). The criteria for an antidromic response illustrated in Fig.24 include: constant latency at threshold stimulation (A); high-frequency-following at 200Hz or above as tested with paired-pulse stimulation (B); collision of spontaneously active spike with an antidromically evoked spike (C-D). The

FIGURE 23

Coronal sections of the rat brainstem region showing the locations of the stimulation sites (filled triangles) from which antidromic responses were elicited in the neurones recorded in the subpallidal area. Note the location of the stimulation sites were mainly around the medial aspect of the PPN and the lateral sector of the central gray area. Abbreviations: BC, brachium conjunctivum; PVG, periventricular gray; PPN, pedunculopontine nucleus; ICO, inferior colliculus; SCO, superior colliculus.

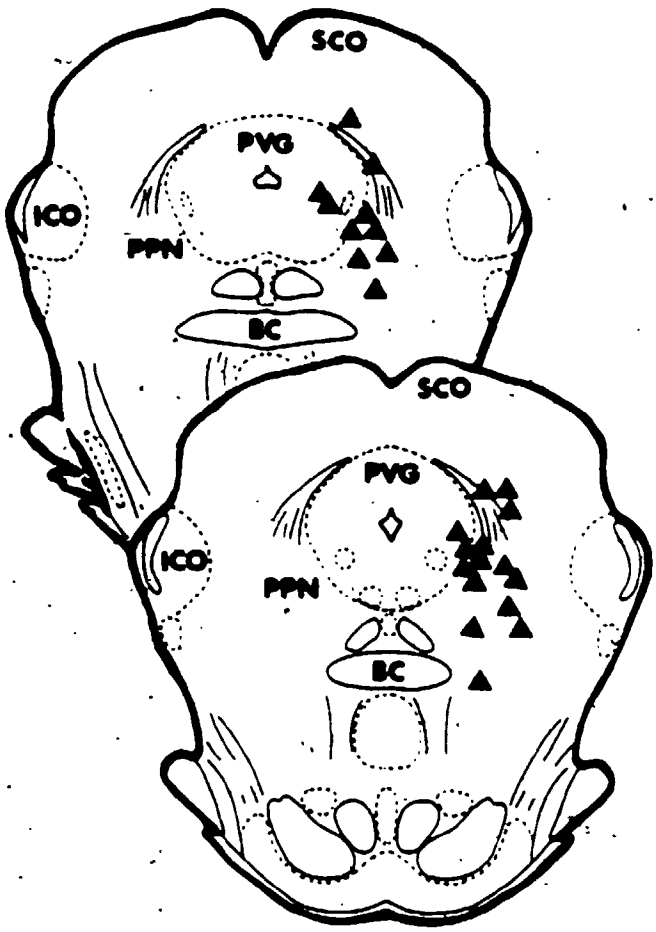

SCO
PVG
ICO
PPN
BC
SCO
PVG
ICO
PPN
BC

FIGURE 24

Microelectrode recordings of an antidromic response from a SP neurone following stimulation of the PPN illustrating the criteria used for identification of an antidromic response.

A: All-or-nothing response of the SP neurone to threshold current stimulation of PPN. Current pulses (400uA;0.15m duration) were delivered at the time indicated by the arrow heads (SPPN). The onset latency of the antidromic response was 5 ms.

B: Another criteria for the antidromic response of this SP neurone to PPN stimulation is the high-frequency-following as tested by paired-pulses stimulation of the PPN. This neurone followed high frequency stimulation to 770 Hz (with inter-pulse interval=1.3 ms).

C and D: Collision test for antidromic response : as a spontaneously active spike fell within the 'critical period' it 'collided' with the antidromic spike evoked by PPN stimulation. All photographs were taken from 7 sweeps. Calibration scale: 100uA, 2ms.

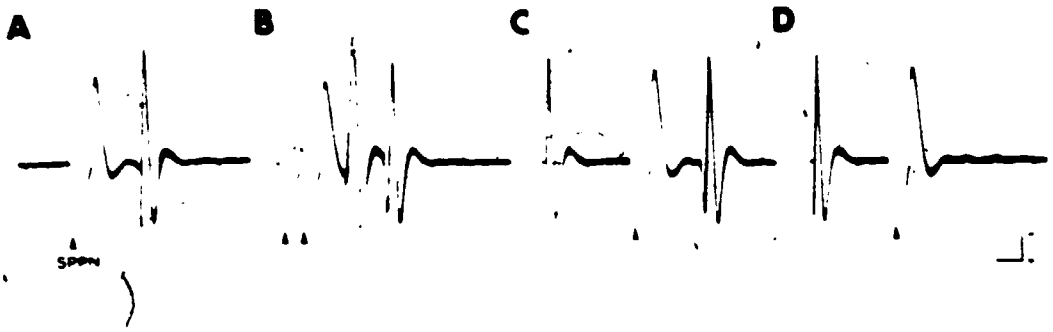
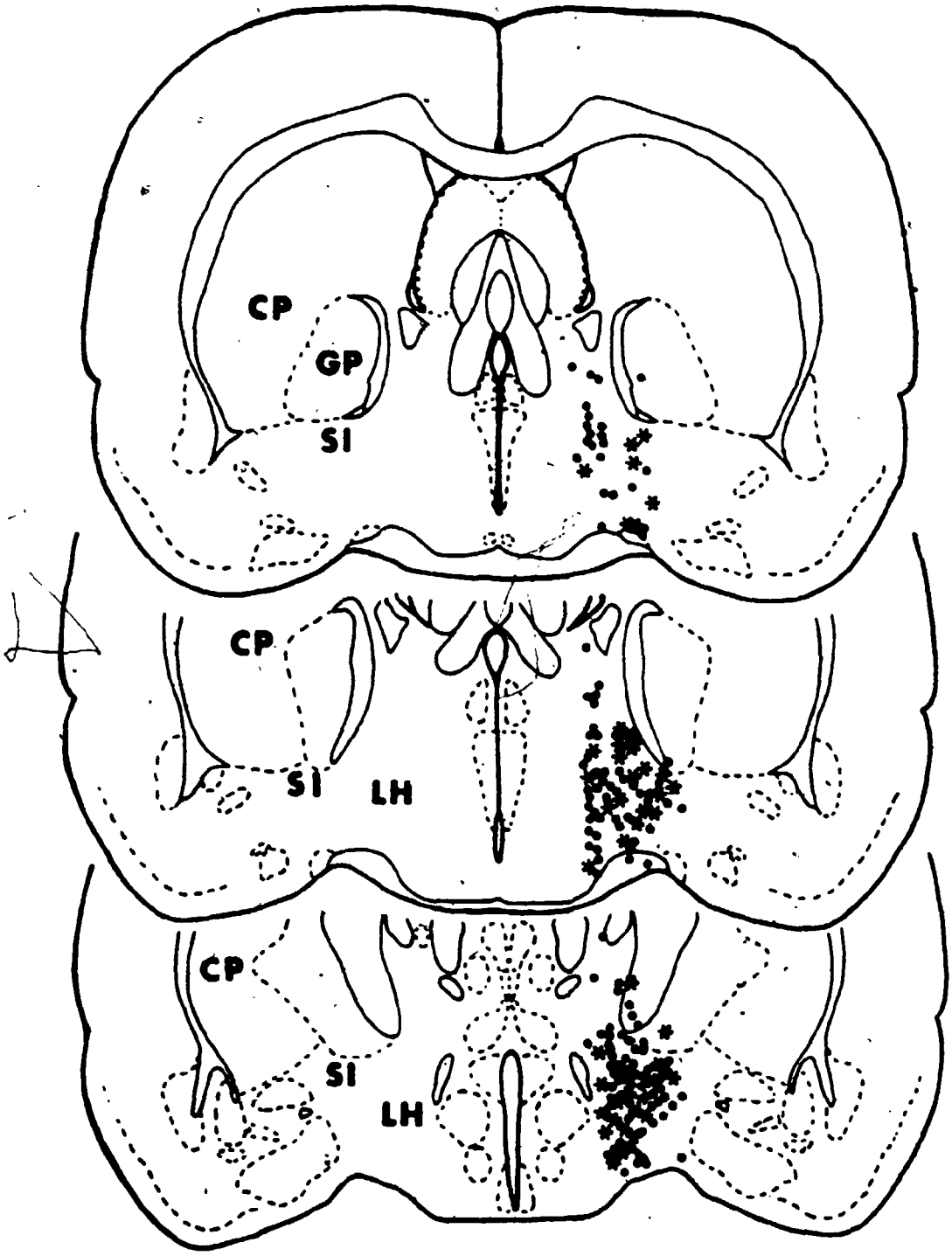

A
B
C
D
SPDN

FIGURE 25

Successive coronal sections of the subpallidal region (SP) of the rat brain showing microelectrode recording sites of neurones antidromically activated by the stimulation of PPN. Closed circles (●) indicate silent SP neurones antidromically activated by PPN stimulation. Asterisks (*) indicate the locations of spontaneously discharging SP neurones which were also activated antidromically by PPN stimulation. The spontaneous activity of the same neurones were also inhibited orthodromically by the stimulation of the ventral subiculum of the hippocampus. Abbreviations: CP, caudate-putamen complex; GP, globus pallidus; SI, substantia innominata; LH, lateral hypothalmus.


CP
GP
SI
CP
SI
LH
CP
SI
LH

recording sites of these neurones were primarily in the sublenticular portion of the substantia innominata and the lateral hypothalamus shown in Fig.25. Forty seven of the 229 SP neurones (21%) were spontaneously active and they were also inhibited orthodromically by hippocampal stimulation (Fig.26A). The discharge rate of this group of SP neurones was slower (15-20 Hz)than those SP neurones (25-40 Hz) not activated antidromically by PPN stimulation. Furthermore, 8(3%) SP neurones were excited by the hippocampal stimulation.

Seventy-six percent of the SP neurones (174 of 229), activated antidromically by PPN stimulation were silent (Table 9). They satisfied the criteria of constant onset latency at threshold PPN stimulation and high frequency following (200 Hz or above). For these silent neurones, the collision test for antidromic responses could not be used. Furthermore, it was not possible to determine whether these neurones were inhibited by orthodromic hippocampal stimulation. The mean onset latencies of antidromic responses of these silent SP neurones to PPN stimulation were distributed bimodally (Fig.27) with the majority from 12-15 ms. The estimated mean conduction velocity of these SP-PPN neurones was 0.5m/s. The mean onset latency of the antidromic responses of the spontaneously active SP neurones to PPN stimulation was shorter (6.2 ms) and with an estimated conduction velocity of 1.2 m/s.

FIGURE 26

Peristimulus time histograms showing the effects of microinjection of LY171555, a dopamine D-2 agonist, into the accumbens and the changes of the inhibitory responses of a SP-PPN neurone to hippocampal stimulation following this injection.

A: Inhibitory responses of a subpallidal neurone to hippocampal stimulation (500uA, 0.15ms duration, at 1.0 Hz) and its antidromic response to PPN stimulation (400uA, 0.15ms duration at 1.0 Hz). Hippocampal stimulation was delivered at the time indicated by an arrow(SH) and the antidromic stimulation of PPN was delivered at the period indicated by a second arrow (SPPN). The onset latency of the inhibitory response to hippocampal stimulation occurred at 22 ms, while the onset latency of the antidromic response of the same SP neurone to PPN stimulation occurred at 8 ms. AR indicates the antidromic response appeared in the histogram.

B: Preinjection control inhibitory response of the same SP neurone to hippocampal stimulation.

C: 5 min after the microinjection of LY171555 (2.0ug/0.2ul), a dopamine D-2 agonist, into the medial nucleus accumbens, the inhibitory response was reduced when compared to the pre-injection control respopse in (B).

D: Recovery of the inhibitory response of the same SP neurone to hippocampal stimulation. 45 min after the drug injection.

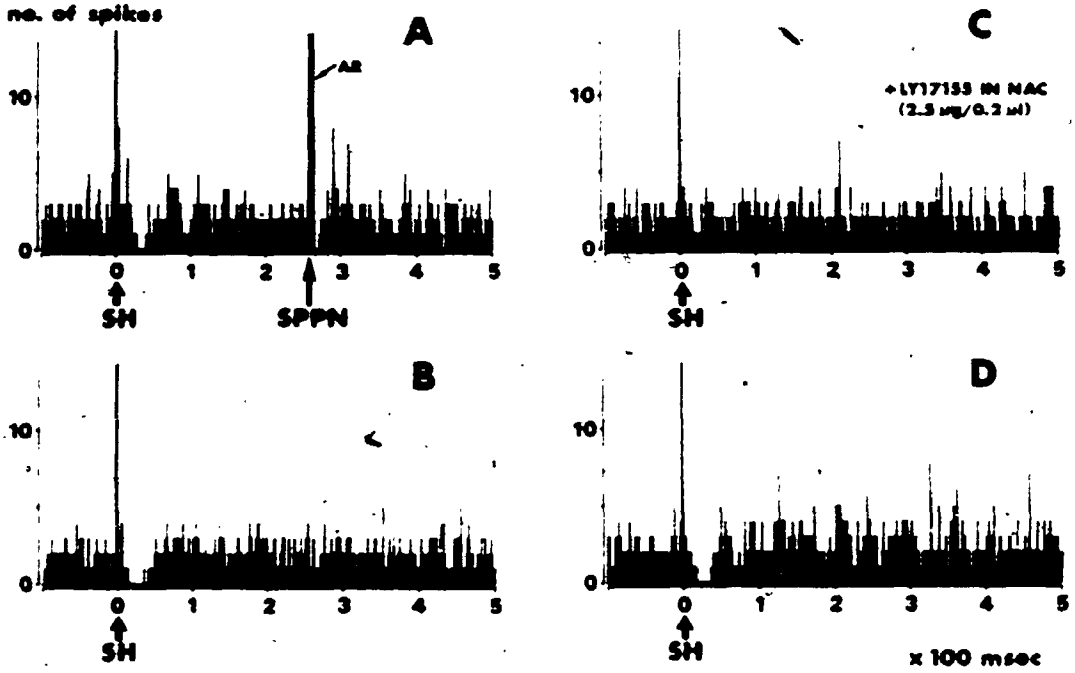
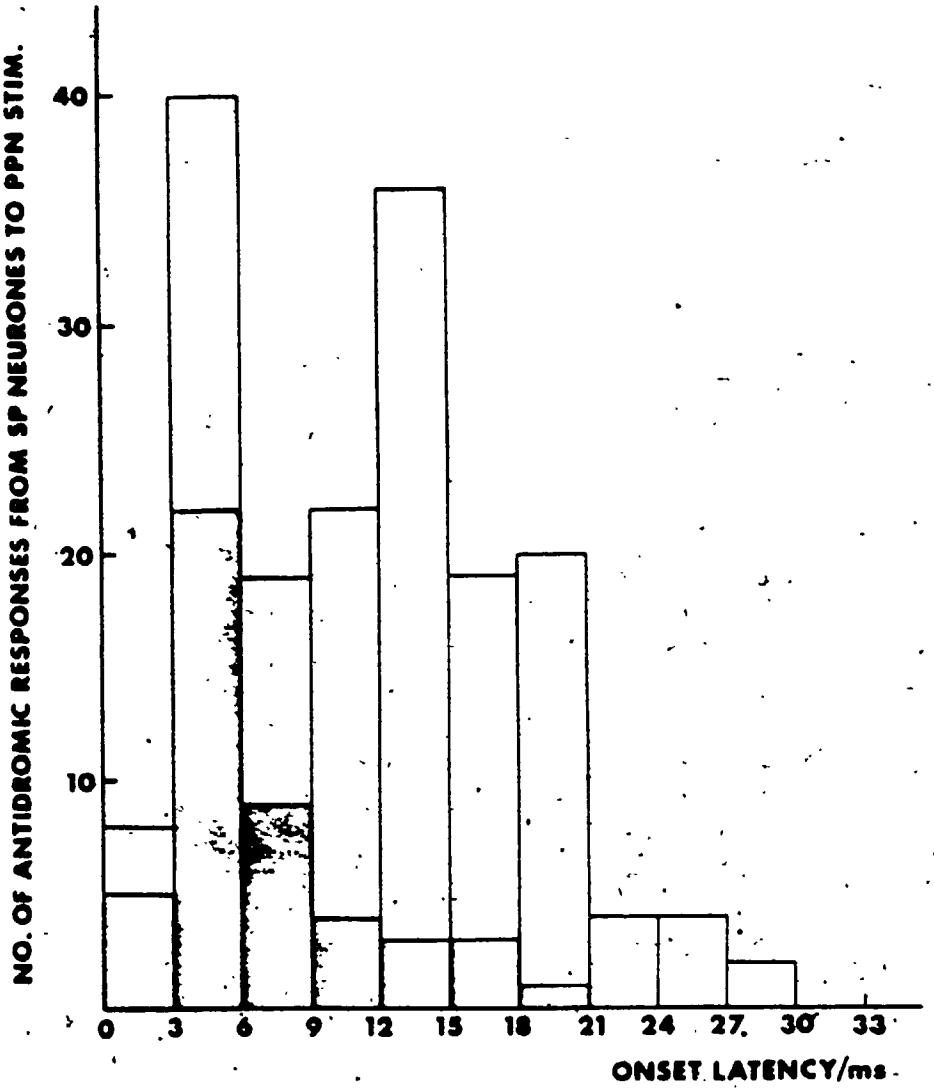

no. of spikes
A
AR
10
0
0 1 2 3 4 5
SH
SPPN
C
+LY17153 IN NAC
(2.5 mg/0.2 ml)
10
0
0 1 2 3 4 5
SH
B
10
0
0 1 2 3 4 5
SH
D
10
0
0 1 2 3 4 5
SH
x 100 msec

FIGURE 27

Histograms showing the distribution of the onset latencies of the antidromic responses of silent and spontaneously active SP neurones to PPN stimulation. Open bar histograms indicate the distribution of onset latencies of the antidromic responses of 118 silent SP neurones to PPN stimulation. Note the apparent bimodal distribution of the onset latency with one group of neurones having a shorter latency in the 3-6 ms range and the other group having a longer latency at 10-15 ms range. The shaded histograms represent onset latencies of antidromic responses of spontaneously discharging SP neurones to PPN stimulation. These same neurones were also inhibited orthodomically when the ventral subiculum of the hippocampus was stimulated. Note that most of these SP-PPN neurones have shorter antidromic latency in the range of 3-6 ms.


NO. OF ANTIDROMIC RESPONSES FROM SP NEURONES TO PPN STIM.
40
30
20
10
0
3
6
9
12
15
18
21
24
27
30
33
ONSET LATENCY/ms

Seventy-two of the 80 (90%) spontaneously active SP neurones (25-40 Hz), not antidromically activated by PPN, were inhibited orthodromically by threshold stimulation of the ventral subiculum of the ipsilateral hippocampus (200-800 uA, 0.15 ms duration at 1.0 Hz) and 8 (10%) were excited (Table 9). The mean onset latencies of the inhibitory responses were 19 ms (range:12-26 ms) and the excitatory responses were 14 ms (range:7-26ms).

4.2 Effects of Dopamine D-1(SKF38393) and D-2(LY171555) Agonists Injected Into the Nucleus Accumbens on the Inhibitory Responses of SP Neurones to Hippocampal Stimulation.

The effects of injections of dopamine D-1 and D-2 agonists made sequentially into the medial accumbens on the inhibitory responses of SP neurones to hippocampal stimulation were studied. Fourteen spontaneously discharging SP neurones, antidromically activated by PPN stimulation, were classified as output neurones to the PPN (SP-PPN neurones). The orthodromic inhibitory responses of these neurones to threshold hippocampal stimulation were then assessed quantitatively. The same period of inhibition (expressed as percentage of inhibition of baseline firing) before, and after sequential injections of SKF38393 (2ug/0.2ul) and LY171555 (2ug/0.2 ul) into the accumbens was assessed. The inhibitory responses were not changed when the D-1 agonist was injected into the accumbens. When the

Table 9. A summary of the responses of subpallidal neurones to hippocampal and PPN stimulation.

	Responses of Subpallidal Neurones to Hippocampal Stimulation			
	Inhibited	Silent	Excited	Total
Number of Neurones	72 (90%)	-	8 (10%)	80 (100%)
Antidromically Activated By PPN Stimulation	47 (21%)	174 (76%)	8 (3%)	229 (100%)
Tested With Microinjection Into The Nucleus Accumbens Of:				
A) SKF38393 (D-1)	<u>18</u> + 10	–	–	–
B) LY171555 (D-2)	<u>15</u> + 10	–	–	–
C) SKF38393, & LY171555 Sequentially	<u>14</u>	–	–	–

The numbers underlined represent inhibitory responses of SP-PPN neurones tested with microinjection of the dopamine D-1 and D-2 agonists into the accumbens.

dopamine D-2 agonist, LY171555, was injected into the accumbens, the inhibitory response of the same SP neurone to hippocampal stimulation was attenuated. A typical response from one SP neurone is illustrated in Fig.28 (and also in Fig. 26B-D). In 3 of these 14 SP-PPN neurones the 2 agonists were injected into the accumbens in reverse order, that is, LY171555 was injected before SKF38393. The inhibitory responses of the SP-PPN neurones to hippocampal stimulation were attenuated by LY171555 injection for periods up to 40-50 min. There were no changes in the inhibitory response after injection of SKF38393.

The effects of injections of the D-1 agonist, or the D-2 agonist into the medial accumbens on the inhibitory responses in 2 separate groups of SP-PPN neurones to hippocampal stimulation were also studied. Significant difference [2-way mixed model ANOVA, between group variation, $F(1,31)=18.8$, $p<0.0005$] was found when the inhibitory responses from 18 SP-PPN neurones after injection of LY171555 into the accumbens were compared with the inhibitory responses from another 15 SP-PPN neurones after the injection of SKF38393 into the accumbens (Fig. 29A). There was also significant interaction [$F(1,31)=8.96$, $p<0.01$] which indicated that the injection of the D-2 agonist (LY171555) into the accumbens attenuated the inhibitory responses of the SP-PPN neurones to hippocampal stimulation.

FIGURE 28

Graph showing differential effect of SKF38393 and LY171555 injected into the nucleus accumbens on the inhibitory response of a SP neurone to hippocampal stimulation. Open circles (O) represent the inhibitory response of this SP neurone to hippocampal stimulation not being affected by microinjection of SKF38393 (2.0ug/0.2ul), a D-1 agonist, into the accumbens during the 15 min post-injection period. Filled triangles (▲) indicate a progressive reduction of the inhibitory response following injection of LY171555 (2.0ug/0.2ul), a dopamine D-2 agonist, into the accumbens during another 15 min post-injection period.

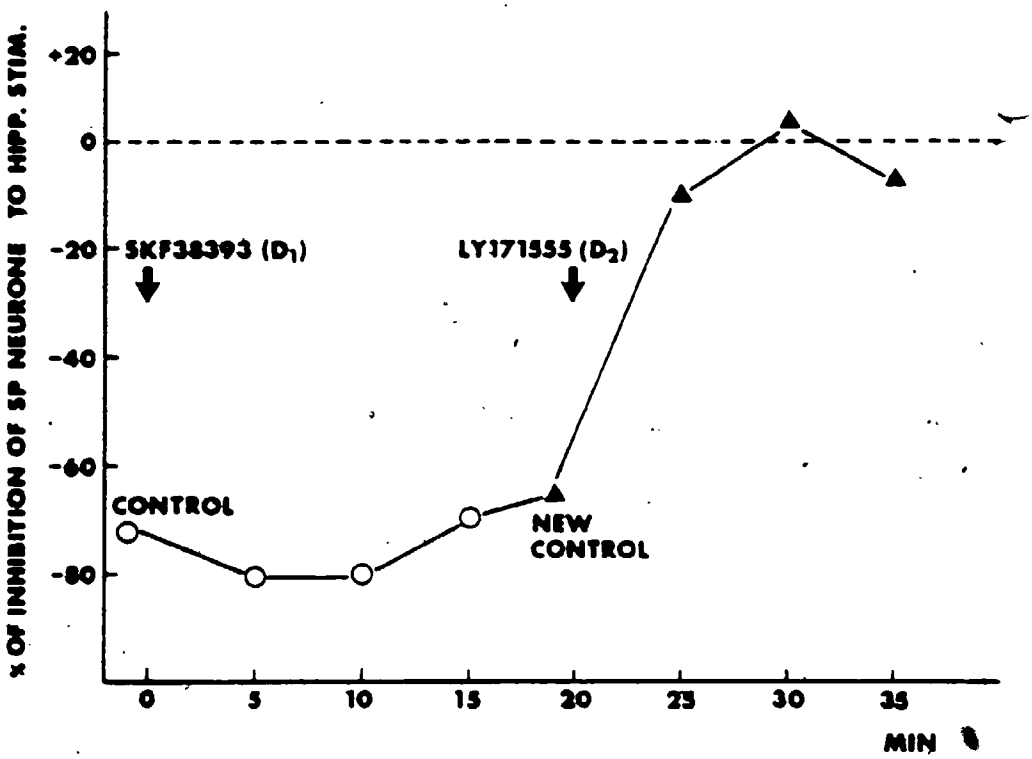
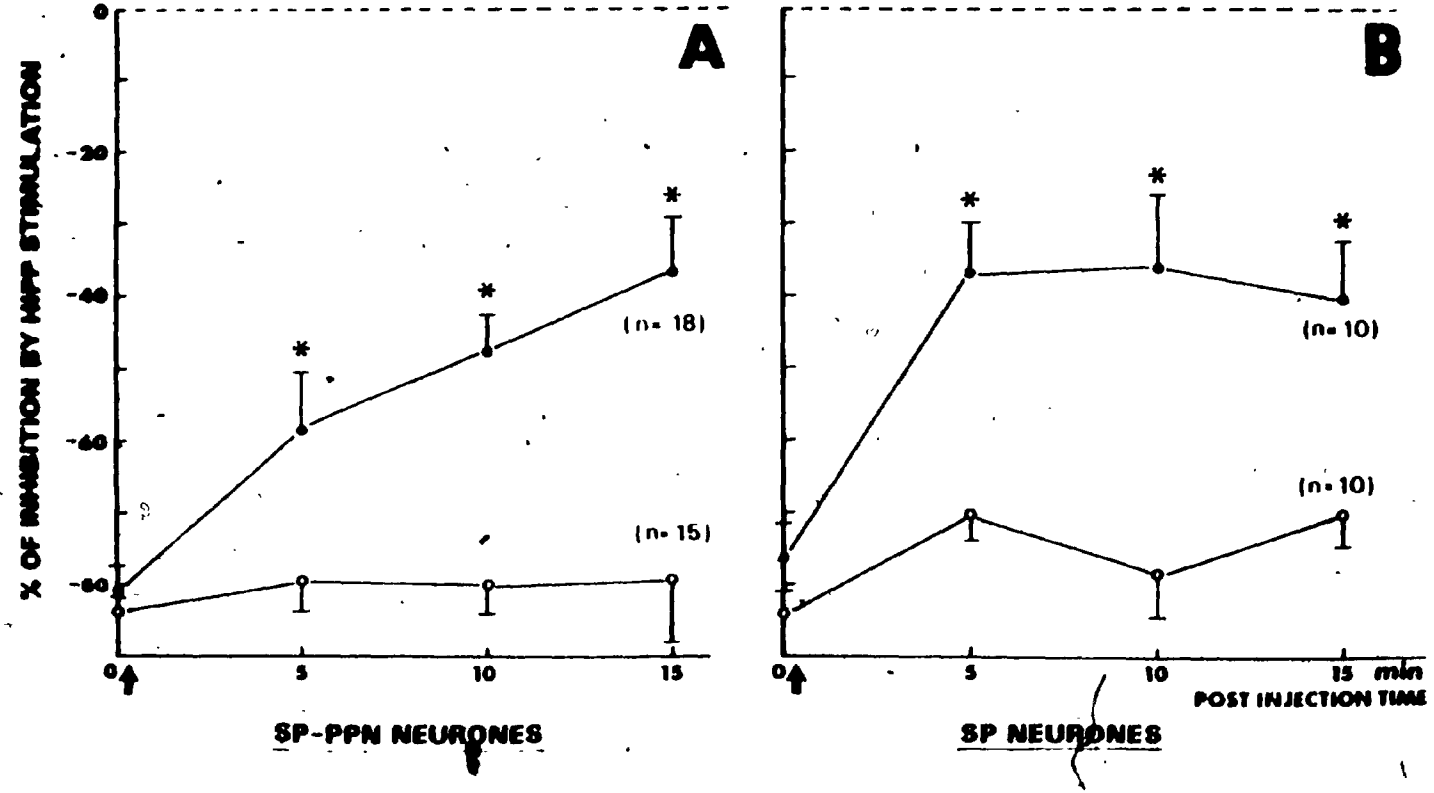

% OF INHIBITION OF SP NEURONE TO HIPP. STIM.
+20
0
-20
-40
-60
-80
SKF38393 (D_1)
LY171555 (D_2)
CONTROL
NEW CONTROL
0
5
10
15
20
25
30
35
MIN

FIGURE 29

Graphs showing the changes of the inhibitory responses in separate groups of A) SP-PPN neurones and, B) SP neurones to hippocampal stimulation after separate injections of the D-1 agonist, SKF38393 (2ug/0.2ul), or the D-2 agonist, LY171555 (2ug/0.2ul). Control responses were taken at 0 min and the time of the injection is indicated by the arrow. Responses from the D-1 agonist injected groups are represented by open circles (0). Responses from the D-2 agonist injected groups are represented by filled circles (0). * indicates significant differences at $p<0.001$ level.


A
B
% OF INHIBITION BY HPP STIMULATION
0
-20
-40
-60
(n= 18)
(n= 15)
(n= 10)
(n= 10)
0
5
10
15
min
POST INJECTION TIME
SP-PPN NEURONES
SP NEURONES

4.3 Effects of Microinjection of Dopamine D-1 and D-2 Agonists Into The Accumbens On the Inhibitory Responses of SP Neurones to Hippocampal Stimulation.

A similar comparison of the effects of SKF38393 and LY171555 with 2 groups of 10 spontaneously active SP neurones which were inhibited by hippocampal stimulation but were not activated antidromically by PPN stimulation was made. Significant differences [$F(1,18)=8.47$, $p<0.02$] was found when the inhibitory responses from 10 SP neurones after injection of LY171555 into the accumbens was compared with another 10 SP neurones after injection of SKF38393 into the accumbens (Fig. 29B).

4.4 Effects of Microinjection of N-Methyl-D-Aspartatic Acid(NMDA) Into the Hippocampus and Of a D-2 Agonist Into the Nucleus Accumbens On Locomotor Activity.

Unilateral microinjections of NMDA (0.5ug/0.2ul) into the ventral subiculum of the hippocampus produced up to a three-fold increase in overall locomotor activity (Fig.30,32,34). This dose of NMDA was chosen, in preliminary experiments, on the basis of its maximum effect in producing a change in locomotor response above baseline activity but below threshold for seizure activity. Increased sniffing and exploration of corners of the activity box were also observed during the post-injection period. This hyperkinetic effect lasted for at least 10 mins and in some rats the NMDA-induced activity lasted for up to 30 mins post-injection. Microinjection of the D-2 agonist,LY171555 (1.0-

4.0 ug) into the medial accumbens prior to NMDA injection into the hippocampus, significantly reduced the hyperkinetic response in a dose-dependent manner [$F(3,25)=3.1, p<0.05$] (Fig. 31). Since significant differences among the means of the NMDA-induced locomotor response after injection of LY171555 into the accumbens were found, a Neuman Keul's test was conducted. From this test, it was found that all three dosages of LY171555 significantly ($\alpha<0.05$) reduced the NMDA-induced locomotor response. This NMDA-induced hyperkinetic response also appeared to be reduced by the injection of LY171555 into the contralateral accumbens but the reduction was not statistically significant [$F(3,20)=1.82$, $p>0.1$]. By itself, however, the D-2 agonist at the 3 chosen dosages did not reduce locomotor activity as compared to the baseline or saline control ($n=8$ rats, 16 injection sites)(Fig. 31).

In preliminary experiments, the influences of microinjections of two other excitatory amino acid receptor agonists, kainic acid (2ng/0.2 ul) and quisqualic acid (0.5ug/0.2 ul) into the hippocampus were also studied. In 5 rats tested seizures and convulsive activities were observed even at the lowest dose (2ng) so that these experiments had to be discontinued.

FIGURE 30

Effects of microinjection of LY171555, a dopamine D-2 agonist, into the nucleus accumbens on the locomotor activity induced by microinjection of NMDA into the ventral subiculum of the hippocampus. Inset: schematic diagram of a saggital section of the rat brain illustrating the locations of the injection cannulae in the hippocampus (through which NMDA was injected to activate the hippocampal-accumbens pathway), and in the medial nucleus accumbens (through which LY171555, the dopamine D-2 agonist, was injected). The time course of locomotor response before and after drug injections into the hippocampus and the nucleus accumbens are shown. Open circles (O--O) indicate the mean locomotor activity counted as photobeam interruptions in each minute before and after saline injection to both brain sites. Filled circles (●—●) indicates the locomotor activity before and after NMDA injection into the hippocampus and saline injected into the accumbens. Note the 2- to 3- fold increase in overall locomotor activity compared to baseline pre-injection or saline control responses. Filled diamonds (◆···◆) indicate the locomotor response before and after LY171555 (4.0 ug/0.2ul) injection into the accumbens prior to NMDA injection into the hippocampus. Each symbol represents the mean score in locomotor response and bars showing S.E.M. were drawn in one direction for clarity. Arrow in the bottom indicates the time when drug injection occurred. Data on the left side of the arrow represent pre-injection locomotor responses and data on the right side of the arrow are post-injection responses (n=8 rats, 16 injection sites).

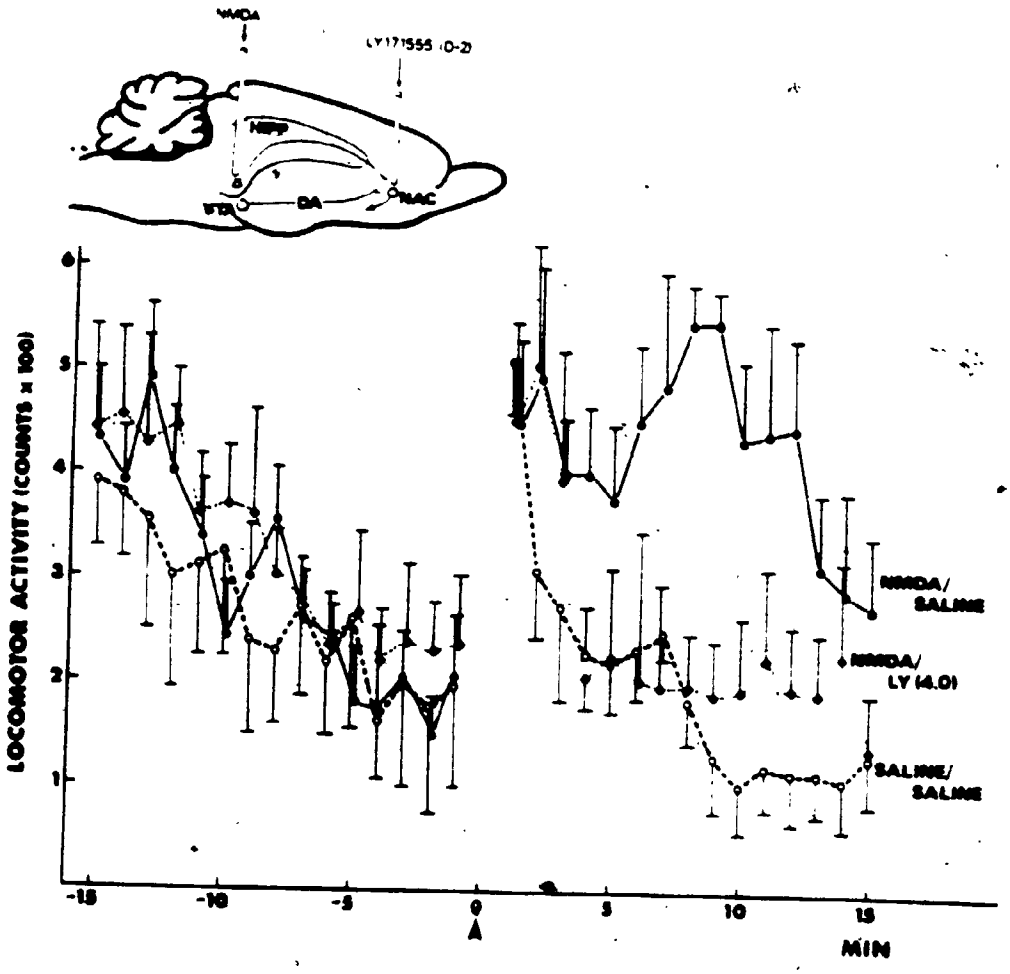
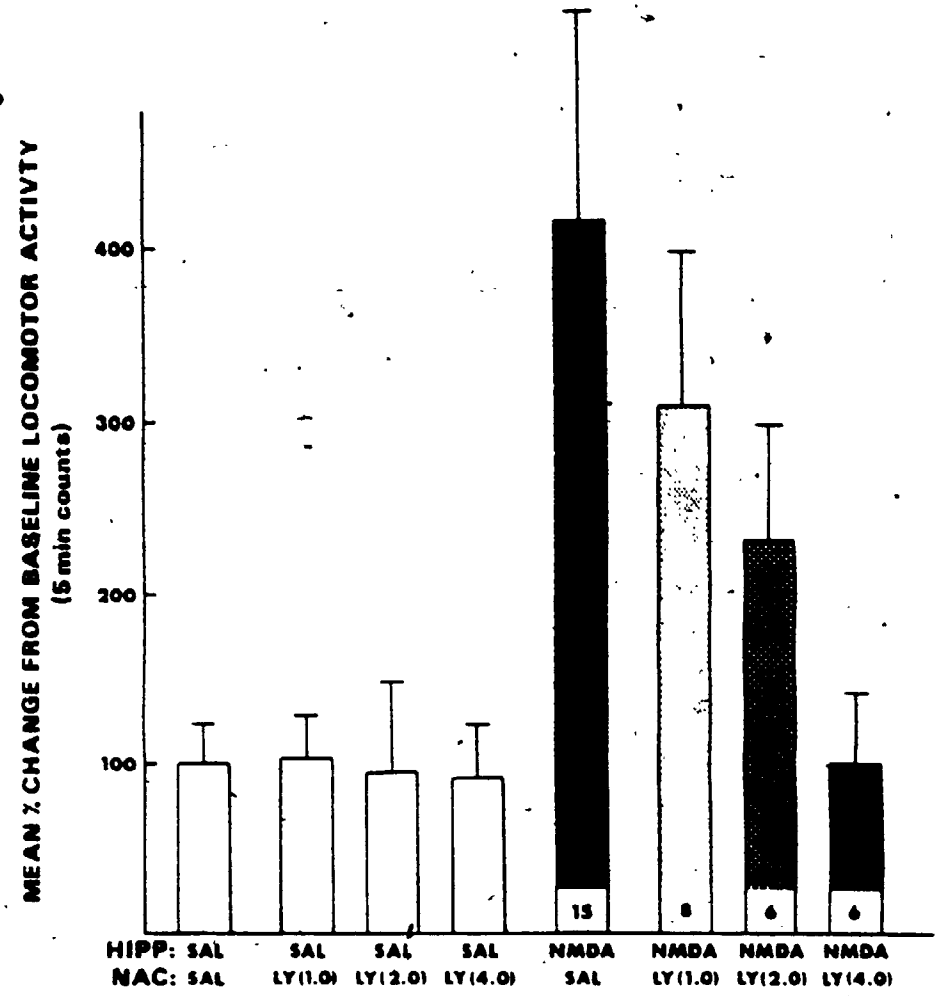

NMDA
LY171555 (0-2)
NMDA/
SALINE
NMDA/
LY (4.0)
SALINE/
SALINE
LOCOMOTOR ACTIVITY (COUNTS x 100)
MIN

FIGURE 31

Locomotor activity elicited by NMDA injection into the hippocampus was reduced in a dose-dependent manner when LY171555 was injected into the accumbens prior to NMDA injection. The histograms illustrate the mean activity occurring between 5-10 min post-injection expressed as a percentage of the mean baseline activity taken from the last 5 min before drug injection. The numbers at the bottom of the histograms indicate the number of injection sites and they are also corresponded to the same numbers of sites in the control groups. The results are expressed as mean±S.E.M. obtained from 16 injection sites in 8 rats.


MEAN % CHANGE FROM BASELINE LOCOMOTOR ACTIVTY
(5 min counts)
400
300
200
100
15
8
6
6
HIPP: SAL SAL SAL SAL NMDA NMDA NMDA NMDA
NAC: SAL LY(1.0) LY(2.0) LY(4.0) SAL LY(1.0) LY(2.0) LY(4.0)

4.5 Effects of Microinjection of Nipecotic Acid Into the Subpallidal Region On the NMDA-Induced Hyperkinetic Locomotor Response.

Unilateral microinjection of nipecotic acid, a GABA-uptake inhibitor into the subpallidal region, including the sublenticular portion of the substantia innominata and the lateral hypothalamus, attenuated the NMDA-induced increase in locomotor activity (Fig.32). By itself,NPA (at 1 and 2ug) did not appreciably change the locomotor activity when compared to the saline control. However, at the highest dose used (4ug) NPA injected into the subpallidal region produced a decrease in baseline locomotor activity when compared to the saline control ($p<0.05$) (Fig.33). In addition, only at doses of 2 and 4ug did NPA produce a dose-dependent reduction of locomotor activity induced by NMDA injection into the hippocampus [$F(3,20)=3.4, p<0.05$] (Fig. 34)(9 rats, 18 injection sites). Neuman-Kuel's test has indicated that NPA at 2 and 4 ug reduced the NMDA-induced locomotor activity significantly ($\alpha<0.05$) while 1ug NPA was ineffective ($\alpha>0.05$). Injection of NPA into the SP contra-lateral to the side of the NMDA injection into the hippocampus did not reduce the hyperkinetic response significantly [$F(3,21)=0.73$, $p>0.2$].

Further experiments were conducted to elucidate whether the hyperkinetic effects produced by NMDA injection into the hippocampus was mediated via the SP. Procaine, a neuronal blocker, injected into the SP reduced significantly ($p<0.01$) the NMDA-induced hyperkinetic responses (Fig. 33).

FIGURE 32

Effects of microinjection of nipecotic acid, a GABA uptake inhibitor, into the nucleus accumbens on the locomotor activity induced by microinjection of NMDA into the ventral subiculum of the hippocampus. Inset: schematic diagram of a sagittal section of the rat brain illustrating the locations of the injection cannula in the hippocampus (through which NMDA was injected to activate the hippocampal-accumbens pathway), and in the subpallidal area(through which nipecotic acid was injected). The time course of the locomotor responses before and after drug injections into the hippocampus and the nucleus accumbens are shown. Open circles (O----O) indicate the mean locomotor activity counted as photobeam interruptions in each minute before and after saline injection to both brain sites. Filled circles (●——●) indicates the locomotor activity before and after NMDA injection into the hippocampus and saline injected into the accumbens. Note the 2- to 3- fold increase in overall locomotor activity compared to baseline pre-injection or saline control responses. Filled diamonds (◆····◆) indicate the locomotor response before and after NPA (4.0 ug/0.2ul) injection into the accumbens prior to NMDA injection into the hippocampus. Each symbol represents the mean score in locomotor response and bars showing S.E.M. were drawn in one direction for clarity. Arrow in the bottom indicates the time when drug injection occurred. Data on the left side of the arrow are pre-injection baseline responses and those on the right side of the arrow represent post-injection responses (n=8 rats, 16 injection sites).

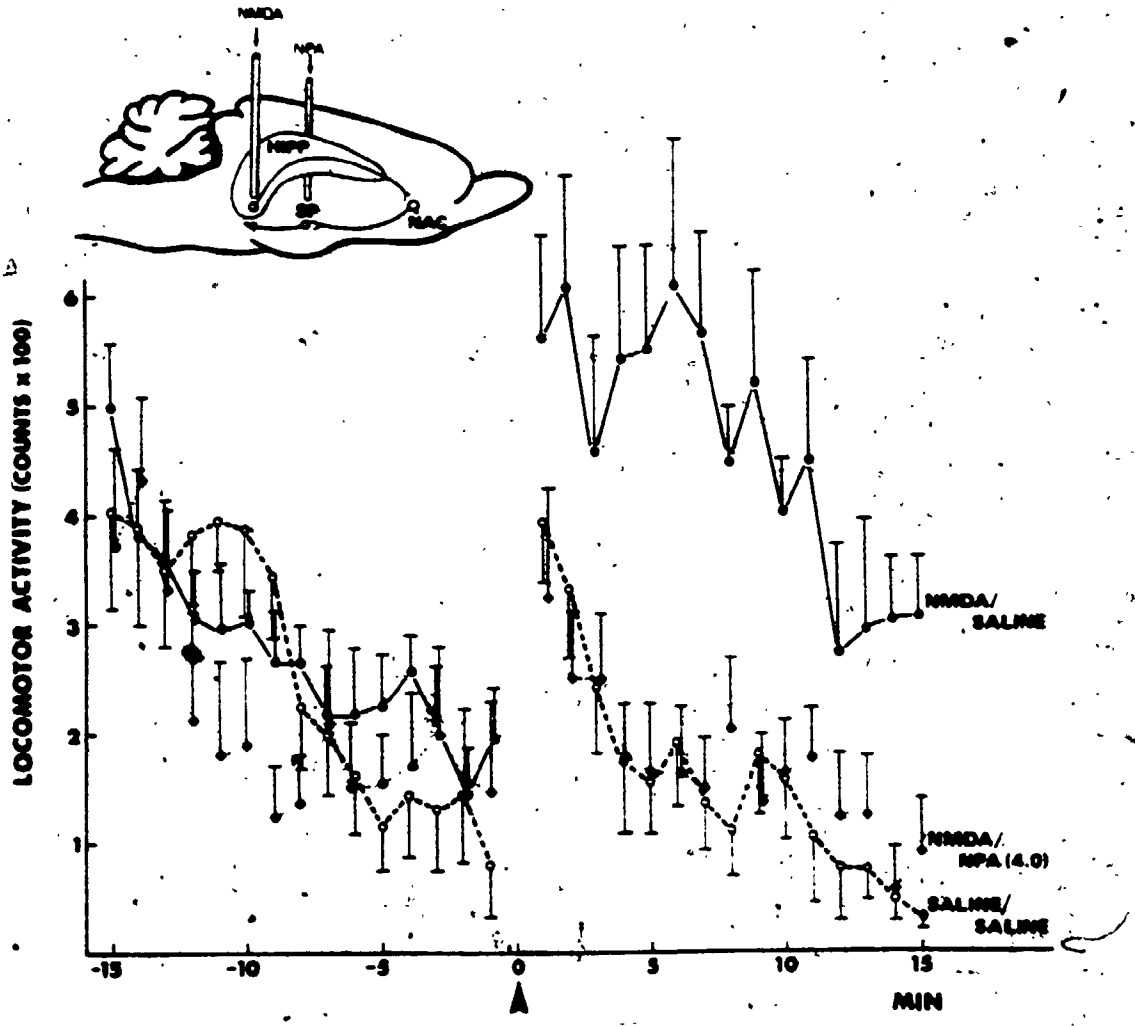
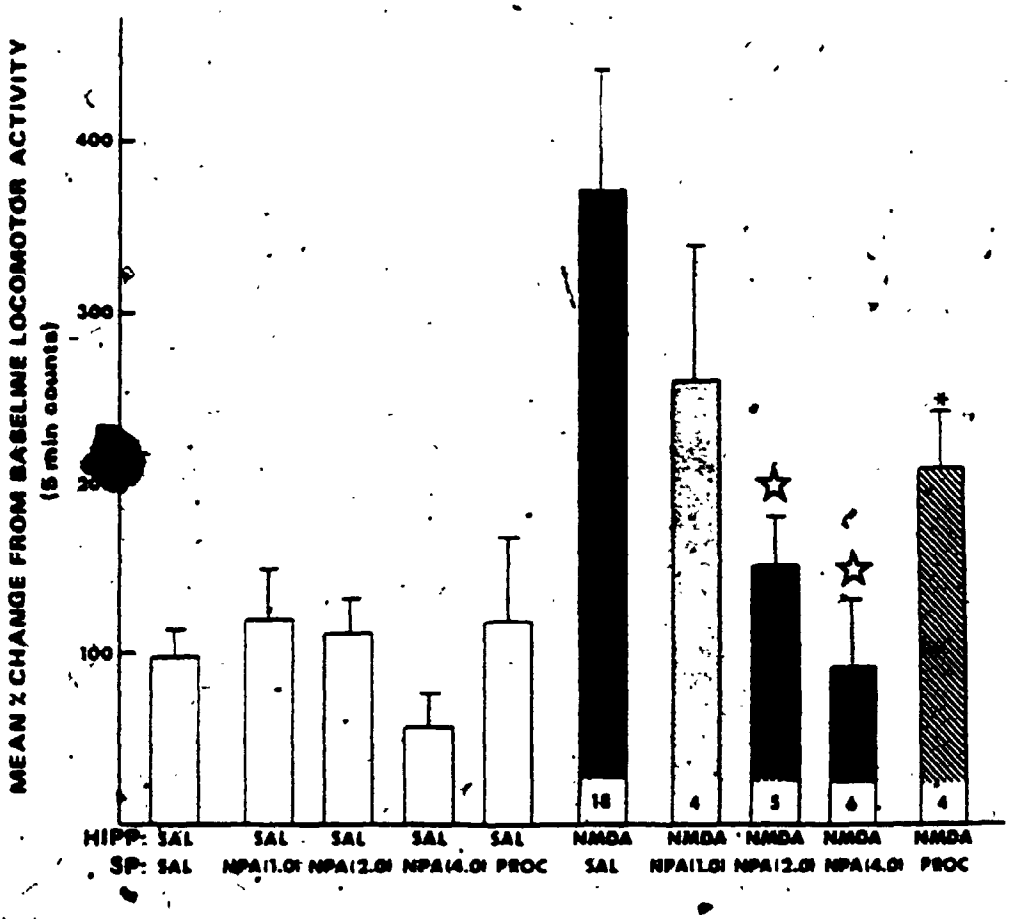

NMDA
NPA
NAC
LOCOMOTOR ACTIVITY (COUNTS x 100)
NMDA/
SALINE
NMDA/
NPA (4.0)
SALINE/
SALINE
-15
-10
-5
0
5
10
15
MIN

FIGURE 33

Locomotor activity elicited by NMDA injection into the hippocampus was reduced in a dose-dependent manner when nipecotic acid (NPA) was injected into the subpallidal area (SP) prior to NMDA injection. Procaine injection into the the SP also attenuated the NMDA-induced hyperkinetic response. The histograms illustrate the mean activity occurring between 5-10 min post-injection expressed as a percentage of the mean baseline activity taken from the last 5 min before drug injection. The results are expressed as mean±S.E.M. and the numbers at the bottom of the histograms indicate the number of injection sites from 9 rats. The open stars indicate $\alpha<0.02$ (Neuman-Kuel's test) when compared to the NMDA/saline control. The asterisk (*) indicates level of significance with $p<0.05$ ('t'-test) when compared to the same NMDA/saline control.


MEAN % CHANGE FROM BASELINE LOCOMOTOR ACTIVITY
(5 min counts)
400
300
100
18
4
5
6
4
HIPP: SAL SAL SAL SAL SAL NMDA NMDA NMDA NMDA NMDA
SP: SAL NPA(1.0) NPA(2.0) NPA(4.0) PROC SAL NPA(1.0) NPA(2.0) NPA(4.0) PROC

4.6 Effects of Microinjection of Procaine Into the PPN On The Hyperkinetic Response Induced by NMDA Injection Into The Hippocampus.

Procaine (30ug/0.2ul) injected into the medial PPN and the adjacent lateral central gray area significantly ($t=2.95$, $p<0.02$) reduced the increased locomotor activity induced by NMDA injection into the hippocampus. As shown in Fig. 34 a single dose of procaine used did not produce as great a reduction of the NMDA-induced locomotor activity when compared to reduction of the NMDA-induced locomotor response obtained from the injection of highest dose of LY171555 (4ug) in the accumbens or NPA (4ug) into the SP regions (Compare Fig. 32 and Fig.34). The NMDA-induced hyperkinetic response was not reduced significantly ($p>0.5$) from the injection of procaine into the PPN contralateral to the NMDA injection side. Furthermore, by itself, procaine did not alter the baseline locomotor activity when compared with the saline control (Fig.35).

In summary, this last series of experiments have shown that subpallidal neurones were antidromically activated by stimulation of the pedunculopontine nucleus and the adjacent central gray area. Some of these spontaneously active neurones were also inhibited orthodromically when the ventral subiculum of the hippocampus was stimulated. Microinjection of dopamine D-2 agonist (LY171555), but not the D-1 agonist (SKF38393), into the accumbens, attenuated the inhibitory responses in these neurones. In the freely-

FIGURE 34

Effects of microinjection of procaine, a neural transmission blocker, into the the PPN, on the locomotor response induced by microinjection of NMDA into the ventral subiculum of the hippocampus. Inset: schematic diagram of a saggital section of the rat brain illustrating the locations of the injection cannulae in the hippocampus (through which NMDA was injected to activate the hippocampal-accumbens neurones) and in the PPN (through which procaine is injected to block the signal transmission elicited by NMDA injection into the hippocampus. The time course of locomotor responses before and after drug injections into the hippocampus and into the PPN are shown. Open circles (O—O) indicate the mean counts of photobeam interruptions triggered from locomotor activity of the animal in each minute before and after saline injection in both hippocampus and PPN. Filled circles (●···●) indicate the locomotor activity before and after NMDA injection into the hippocampus. Note the 2- to 3- fold increase in overall locomotor activity compared to the baseline pre-injection or saline control. Filled diamonds (◆···◆) indicate the locomotor response before and after procaine injection into the PPN prior to NMDA injection into the hippocampus. The arrow at the bottom indicates the time when drug injection occurred. Responses on the left side of the arrow were preinjection baseline locomotor responses and those to the right side of the arrow are post-injection responses. Each symbol represents the mean score in locomotor response and bars showing S.E.M. were drawn in one direction only for clarity.

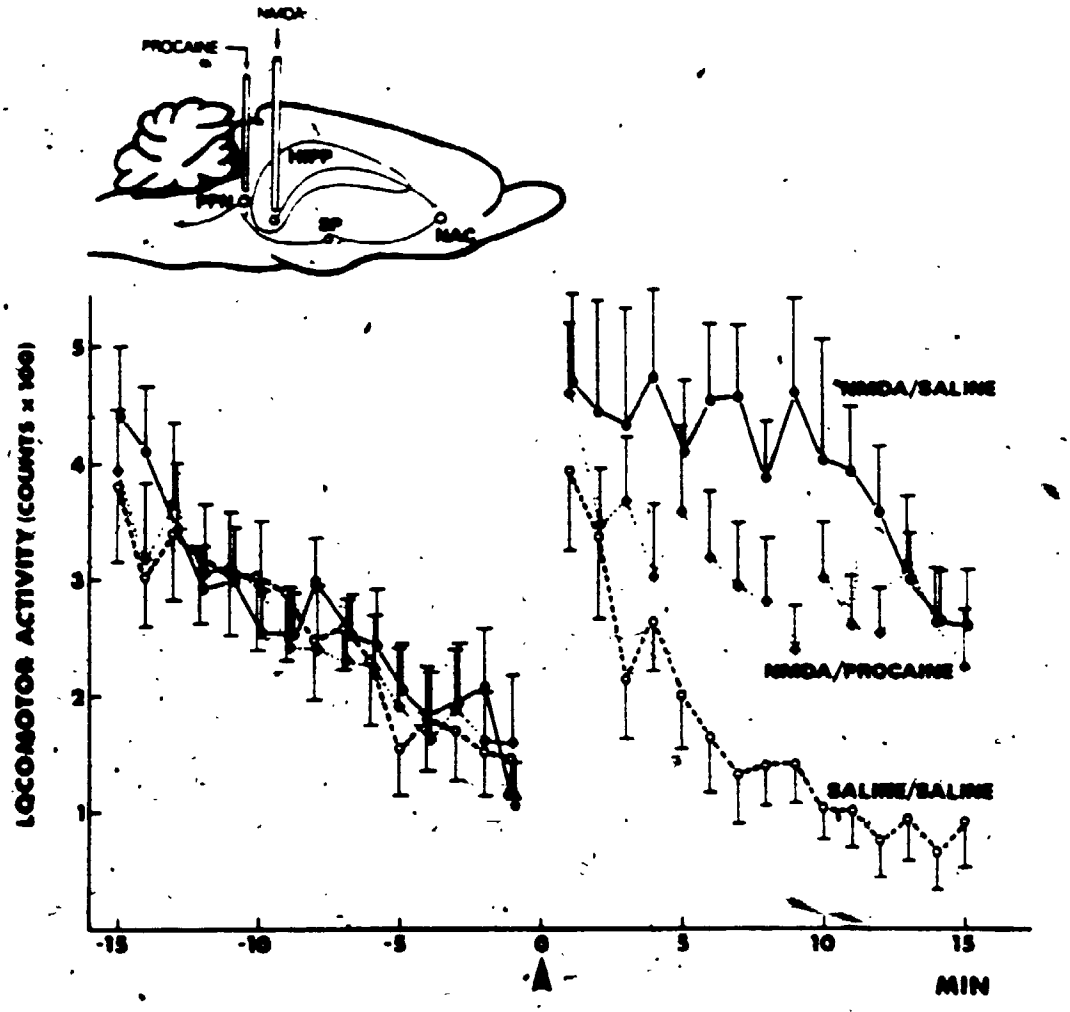
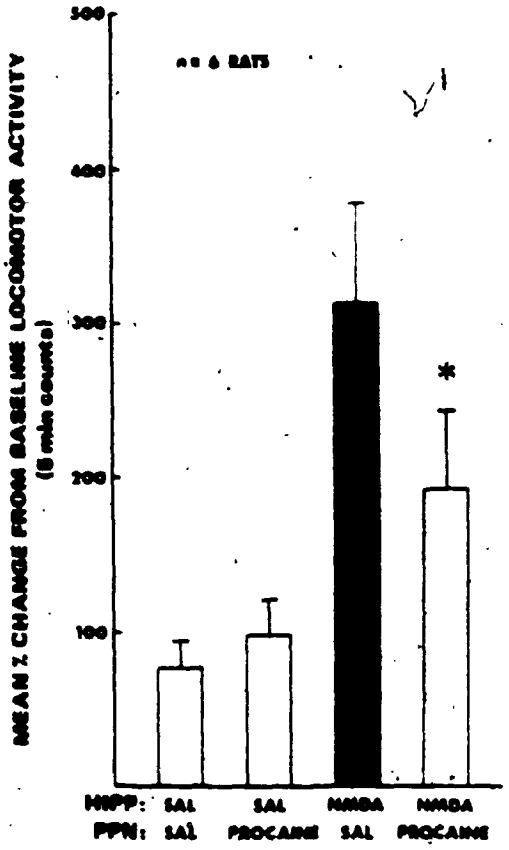

NMDA
PROCAINE
HIPP
PPN
SP
NAC
LOCOMOTOR ACTIVITY (COUNTS x 100)
5
4
3
2
1
-15
-10
-5
0
5
10
15
MIN
NMDA/SALINE
NMDA/PROCAINE
SALINE/SALINE

FIGURE 5

Histograms showing the influence of procaine on the hyperkinectic response produced by NMDA injection into the hippocampus. Unilateral injection of procaine (30ug/0.2ul) into the PPN prior to NMDA injection into the ventral subiculum of the hippocampus significantly reduced the NMDA-induced locomotor activity.. The results are expressed as mean±S.E.M. and 12 pairs of injection sites from 6 rats were explored. * indicates the level of significance at $p<0.02$ level.


MEAN % CHANGE FROM BASELINE LOCOMOTOR ACTIVITY
(5 min counts)
n = 6 RATS
500
400
300
200
100
*
HIPP: SAL SAL NMDA NMDA
PPN: SAL PROCAINE SAL PROCAINE

moving rats injection of NMDA, an excitatory amino acid, into the ventral subiculum increased locomotor response by approximately three fold compared to their baseline or saline control. Injection of the D-2 agonist into the accumbens reduced this hyperkinetic responses dose-dependently. Injection of nipecotic acid, a GABA uptake inhibitor, into the subpallidal region, or procaine, a neuronal blocker, into the SP or PPN and the adjacent central gray, also reduced significantly the hippocampal-induced hyperkinetic responses.

DISCUSSION

The major findings in the series of experiments reported in this thesis are that electrical stimulation of the ventral subiculum of the hippocampus influences the firing rates of neurones recorded in the nucleus accumbens as well as in the subpallidal areas. The majority of neurones in the accumbens were excited while neurones in the subpallidal area were inhibited by hippocampal stimulation. Activation of the converging mesolimbic dopaminergic input to the accumbens by conditioning stimulation of the VTA with trains of 10 Hz pulses, but not by a single-pulse, attenuated the excitatory responses of accumbens neurones. This prolonged attenuating effect appears to be dopamine-mediated since it was reversed by dopamine antagonists, by 6-hydroxydopamine lesions of the VTA, and the effect was mimicked by iontophoretic application of dopamine. Dopamine, via a D-2 receptor-mediated mechanism, enhanced the terminal excitability of hippocampal-accumbens neurones and thus probably produced presynaptic inhibition of the excitatory transmission of the output signals from the hippocampus. This presynaptic D-2 mechanism may constitute part of a gating influence of dopamine in regulating hippocampal throughput in the accumbens.

More accumbens neurones received hippocampal signals relayed monosynaptically to the ventral globus pallidus than to the subpallidal area although both pallidal areas

received hippocampal signals via the accumbens. Some of the same subpallidal neurones, inhibited by hippocampal stimulation, were also activated antidromically by the stimulation of the pedunculopontine nucleus, suggesting a monosynaptic connection of these subpallidal neurones with the mesencephalic locomotor region. Thus, hippocampal signals appear to reach the brainstem MLR site via hippocampus-accumbens-subpallidal-pedunculopontine connections.

Locomotor activity initiated by chemical stimulation of the hippocampus was also attenuated by the injection of a D-2 agonist into the accumbens; or nipecotic acid into the subpallidal area; or procaine into the pedunculopontine nucleus. Results from these experiments have provided further evidence to suggest that hippocampal signals initiating locomotor activity via the accumbens are regulated by a dopamine D-2 mechanism. This gating mechanism in the accumbens modulates hippocampal signal throughput via the nucleus accumbens to the subpallidal area and subsequently to the pedunculopontine nucleus, a part of the mesencephalic locomotor region.

1. Electrophysiological Responses of Neurones in the Nucleus Accumbens to Hippocampal Stimulation.

The majority of neurones in the medial accumbens were activated by stimulation of the ipsilateral ventral subiculum of the hippocampus. The excitatory responses were

recorded from both silent and spontaneously active neurones in the region of the accumbens which has been shown anatomically to receive projections from the ventral subiculum (Groenewegen et al., 1982; Kelley and Domesick, 1982; Swanson and Cowan, 1977). The short onset and duration of these excitatory responses suggests that the pathway connecting the ventral subiculum and the nucleus accumbens is monosynaptic. This suggestion is further supported by the finding that these neurones can be activated antidromically from the stimulation of the medial accumbens and the short onset latency of these antidromic responses were similar to that of the orthodromic excitatory responses of accumbens neurones to hippocampal stimulation (see section 3).

This hippocampal-accumbens projection contains glutamatergic neurones (Walaas and Fonnum, 1979; Walaas, 1981) which appear to mediate the excitatory response. However, iontophoretically applied glutamic acid diethyl ester (GDEE), a glutamate antagonist (Haldeman and McLennan, 1972; McLennan and Wheal, 1976; Watkins and Evans, 1981), blocked only one-half of the excitatory responses of accumbens neurones to hippocampal stimulation. Failure to block more of the excitatory responses may be because of the presence of sub-types of the glutamate receptors which are resistant to GDEE blockade (Watkins and Evans, 1981) or to the presence of excitatory neurotransmitter(s) other than glutamate in the hippocampal-accumbens pathway (Greenwood et

al.,1981). The specificity of GDEE to glutamate receptors has also been questioned (Clark and Straughan,1977).

A small number of neurones in the medio-dorsal accumbens and the adjacent lateral septum, as well as in the ventral accumbens, were inhibited by hippocampal stimulation. The prolonged inhibition of the medio-lateral accumbens could be the result of an activation of inhibitory interneurones by the excitatory hippocampal efferents (DeFrance et al.,1973a;1973b; Fonnum et al.,1979; McLennan and Miller, 1974; Storm-Mathisen, 1977). The onset and duration of the inhibitory responses of the fast-firing ventral accumbens neurones to hippocampal stimulation were also relatively prolonged and may have been mediated by pathways via the entorhinal cortex and external capsule (Chronister et al.,1981; Hjorth-Simonsen and Jeune, 1972). The presence of these fast-discharging neurones delineates the ventral accumbens from the olfactory tubercle as has been reported previously (Yim and Mogenson, 1982).

2. Modification of the Excitatory Accumbens Responses to Hippocampal Stimulation by Dopamine.

The attenuation of the excitatory responses of accumbens neurones to hippocampal stimulation appears to be dopamine-mediated as suggested by three lines of evidence. Firstly, after 6-hydroxydopamine pretreatment to the VTA, significantly fewer accumbens neurones activated by hippocampal stimulation were attenuated by conditioning

stimulation of the VTA. Secondly, the injection of haloperidol or iontophoretic application of trifluoperazine, both dopamine antagonists, significantly reversed the attenuation effect. Thirdly, iontophoretically applied dopamine attenuated the excitatory responses of accumbens neurones to hippocampal stimulation, as well as those excitatory responses which were previously unaffected by stimulation of the VTA which was lesioned by 6-hydroxydopamine. In 9 out of 10 accumbens neurones tested it was observed that the attenuating effect of iontophoretically applied dopamine mimicked that produced by conditioning stimulation of the VTA. Furthermore, iontophoretic application of dopamine or conditioning stimulation of the VTA reduced the number of action potentials of the excitatory responses but not the spike amplitude. This suggests that both exogenously applied dopamine and activation of the VTA neurones have the same effect on the excitatory responses of accumbens neurones to hippocampal stimulation.

Attenuation of the excitatory responses of accumbens neurones to hippocampal stimulation required trains of conditioning pulses delivered to the VTA. The dopaminergic neurones of the VTA (Dahlstrom and Fuxe 1964; Yim and Mogenson, 1982) are known to have a high threshold for excitation and a high stimulation current of 1 mA or above

is required to identify dopaminergic neurones by antidromic stimulation (Deniau et al.,1980; German et al.,1980; Yim and Mogenson, 1980). In this present study, repetitive stimulation of the VTA at 10 Hz with a lower current of 300-700 uA was sufficient to activate these VTA neurones orthodromically.

The synaptic mechanism by which the dopaminergic neurone exerts its attenuating effect on the excitatory responses of accumbens neurones to hippocampal stimulation is unknown. However, we have found in this study that dopamine selectively attenuates the excitatory response of accumbens neurones to hippocampal stimulation but leaves baseline firing of these neurones unchanged. This suggests a presynaptic action of dopamine on the axonal terminals of excitatory hippocampal-accumbens neurones. Dopamine receptors have been localized on the terminals of glutamatergic cortico-striatal neurones (Schwarcz et al.,1978) and the accumbens has been considered as part of the ventral striatum (Heimer and Wilson, 1975). Therefore, one possibility is that dopaminergic fibres inhibit glutamate release from the excitatory allocortico-striatal (hippocampal-accumbens) afferents presynaptically in a way similar to that for the cortico-striatal (cortex-caudate) pathway (Mitchell and Doggett, 1980; Theodorou et al.,1981). On the other hand, findings from recent pharmacological experiments also suggest another interpretation. L-Glutamate

was found to release pre-loaded tritiated dopamine from rat accumbens slices in vitro (Marien et al., 1983). Moreover, behavioural hyperactivity induced by intra-accumbens administration of a glutamate agonist or a dopamine agonist was antagonized by cis-Z-flupentixol, a dopamine antagonist (Arnt, 1981). These observations suggest that there may be an excitatory glutamatergic influence on dopaminergic axonal terminals. The findings in the present series of experiments, nevertheless, favour the earlier suggestion of presynaptic inhibition of excitatory hippocampal afferents by the mesolimbic dopaminergic input in the population of accumbens neurones studied.

An interesting feature of the suppressive effect of dopamine on the excitatory responses of accumbens neurones to hippocampal stimulation was that it persisted for a considerable period of time. This was the case both for the iontophoretic application of dopamine and for conditioning stimulation of the VTA. A long time-course of this duration suggests that dopamine may exert some intracellular metabolic influences in addition to the process of synaptic transmission. Moreover, only with a stimulating or iontophoretic current higher than that necessary to attenuate evoked excitation was there a suppression of both baseline firing together with the excitatory responses of the accumbens neurone. In this condition, dopamine may also

have a post-synaptic inhibitory action on the evoked excitation (Siggins et al.,1974; Woodward et al.,1979). Furthermore, in recent extracellular single unit recording experiments performed in freely-moving monkey, or anaesthetized rats iontophoretically applied dopamine at low delivering current (under 10nA) increased the signal-to-noise ratio of striatal neurone (represented by the increased number of discharges of the neurone during a cortical-meidated behavioural event or glutamate-induced excitation with respect to the background discharge rate of the same neurone), whereas dopamine delivered at higher iontophoretic current (10-35 nA) caused an overall suppression of discharges from the striatal cells (Rolls et al.,1985; Chiodo and Berger, 1986). Conceivably, these post-synaptic striatal processes enable selective transmission of input signals received by the striatum (Rolls et al.,1985; Chiodo, and Berger, 1986). Hence, dependent on how much dopamine is present at the synapse, this catecholamine may act pre-and post-synaptically and influence signal transmission via different modes of actions at multiple synaptic sites (Mecuri et al.,1985).

The major conclusion drawn from this series of experiments is that the attenuation of the excitatory response of the accumbens neurones to hippocampal stimulation by stimulation of the VTA with trains of pulses was dopamine-mediated. The experiments involving

iontophoresis of dopamine, trifluoperazine, and injection of haloperidol and 6-hydroxydopamine support this conclusion.

3. Mechanisms of Dopaminergic Modulation At the Hippocampal-Accumbens Axonal Terminals.

The suggestion that dopamine may have a presynaptic action on the hippocampal-accumbens (HIPP-ACC) neuronal terminal to attenuate the excitatory transmission was investigated by a series of experiments employing the terminal excitability test. Antidromic responses of ventral subicular neurones were first obtained by stimulation of the medial part of the accumbens. The mean onset latencies of these responses were similar to the latencies of the orthodromic excitatory responses of accumbens neurones to stimulation of the ventral subiculum (Lopes da Silva et al.,1984). As indicated earlier, it appears likely that they are glutamatergic neurones (Walaas and Fonnum, 1979a) which originate from the ventral subiculum and terminate in the medial accumbens (Kelley and Domesick, 1982).

The terminal excitability of hippocampal-accumbens (HIPP-ACC) neurones, obtained from threshold stimulation of the accumbens and reflected by their firing index, was enhanced substantially when the VTA was stimulated by trains of conditioning pulses (10 Hz), but single pulses were ineffective. Trains of conditioning pulses to the VTA mimicked the characteristic burst firing pattern of

dopaminergic neurones (Grace and Bunney,1984; Yim and Mogenson, 1980). Such high frequency stimulation of dopaminergic neurones was shown, in a recent study using *in vivo* voltammetry, to produce a larger striatal release of dopamine than that from single pulse stimulation (Gonon and Buda,1985). If the accumbens stimulation current was adjusted to produce a baseline firing index near zero, conditioning stimulation of the VTA did not change the firing index. These observations suggest that dopamine did not tonically influence resting HIPP-ACC neurones, but enhanced their terminal excitability when the glutamatergic synapse was activated (e.g. by a depolarizing current delivered to their terminals via the accumbens electrode)(Nieoullon et al.,1983; Godukhin et al.,1984). Therefore, it appears that some background activity in the terminal of HIPP-ACC neurones is necessary for the subsequent action of dopamine.

Iontophoretic application of dopamine on the axonal terminals of HIPP-ACC neurones also enhanced the firing index of the same neurones but the onset of response to the extrinsic application of dopamine was more gradual. It is possible that the abrupt enhancement of firing index of HIPP-ACC neurones during repetitive VTA stimulation was influenced by other factors, in addition to a genuine dopamine effect. One of the possible factors might include an elevation of extracellular potassium from sustained

neuronal activity resulting from the VTA stimulation (Levy, 1980; Nicoll,1979; Nicoll and Alger,1979; Walz and Hertz, 1984). The enhancement of the firing index of HIPP-ACC neurones to direct iontophoretic application of dopamine has ruled out the possibility that this change in the firing index was produced by the activation of the sparse dopaminergic projection from VTA to the ventral hippocampus (Scatton et al.,1980; Ishikawa et al.,1982). Furthermore, direct application of dopamine hyperpolarizes hippocampal neurones but does not increase their excitability(Bernardo and Prince, 1982a; 1982b; Haas and Konnerth, 1983; Herrling, 1978). This supports the earlier suggestion that VTA stimulation releases endogenous dopamine from the axonal terminals of dopaminergic neurones in the accumbens which enhances the terminal excitability of HIPP-ACC neurones.

In theory, dopamine could enhance the terminal excitability of HIPP-ACC neurones via its D-1 or D-2 receptors (Kebabian and Calne,1978). The sensitivity of the terminals of HIPP-ACC neurones to the D-2 agonist,LY171555, but not to the D-1 agonist, SKF38393, suggests that D-2 receptors mediated the increase in terminal excitability. Furthermore, sulpiride, a selective D-2 antagonist, attenuated the enhanced firing index in these neurones produced by conditioning VTA stimulation while SCH23390, a D-1 antagonist, had no effect.

Whether dopamine, or its D-2 agonist and antagonist, exert their effects directly on the axonal terminals of HIPP-ACC neurones or indirectly via interneurones or via a transynaptic feedback pathway from the accumbens to the hippocampus, was also investigated using ibotenic acid lesions. By administrating this axon-sparing neurotoxin (Kohler and Schwartz, 1983) into the medial accumbens, most of the intrinsic accumbens neurones, as well as the soma of neurones that may feed back to the hippocampus, were destroyed. With this preparation, the firing index of HIPP-ACC neurones following VTA stimulation, iontophoretic application of dopamine or of LY171555 was not significantly different in these rats from that obtained from normal unlesioned rats. These observations provide additional support for the suggestion that direct activation of dopamine D-2 receptors located on the axonal terminals of the glutamatergic HIPP-ACC neurones, but not on intrinsic interneurones in the accumbens or a accumbens-hippocampal pathway, are responsible for the changes in the terminal excitability of HIPP-ACC neurones.

Dopaminergic and glutamatergic neuronal interactions have been studied extensively in the caudate nucleus and some of the findings are relevant to the results of the present study. Dopaminergic agonists (at relatively high doses) decrease the release of glutamate from striatal slices and synaptosomes by high concentration of

extracellular potassium (Mitchell and Dogget, 1980; Rowland and Robert, 1980). Decortication reduced D-2 type dopamine receptor binding in the rat striatum (Schwartz et al., 1980; Theodorou et al., 1981). The striatal release of pre-loaded tritiated glutamate, or excitatory responses of striatal neurones following electrical stimulation of cortical efferents to the striatum is inhibited by conditioning stimulation of the nigrostriatal dopaminergic pathway (Goduhkin et al., 1984; Vives and Mogenson, 1986). These biochemical observations complement the present findings which suggest that D-2 receptors on the afferent terminals of HIPP-ACC neurones modulate the release of glutamate from the axonal terminals by polarizing them. Since the excitability of the HIPP-ACC neurones was also enhanced by extracellular iontophoretic application of potassium, a depolarizing agent, it appears that dopamine may have a depolarizing action. This mechanism is analogous to the well studied phenomenon of primary afferent depolarization responsible for presynaptic inhibition of sensory inputs to the spinal cord (Levy, 1980; Schmidt, 1978; Kocsis and Waxman, 1982). Nevertheless, in electron microscopic studies of the nucleus accumbens, close apposition of the tyrosine hydroxylase-stained (marker for dopaminergic neurones) terminals with striatal afferent to form axo-axonic synapses with post-junctional specialization have not been observed

(Arluison et al.,1984; Hassler and Chung,1976; Pickel et al.,1981). However, dopamine may exert a non-synaptic mode of action over a short distance (200-400 Å, Lehmann and Langer, 1983; Pappas and Waxman,1972; Vizi, 1984) and produce a long-lasting effect. This action of dopamine is thus more appropriately termed 'neuromodulation'(Lehmann and Langer,1983).

The action of dopamine, or its D-2 agonist (LY171555), as well as conditioning VTA stimulation produced a prolonged enhancement of the firing index. Following several brief trains of pulses delivered to the VTA, or short application of the D-2 agonist, recovery did not occur for up to 30 min. For a number of neurones (n=25), no recovery was observed during the entire period of recording, up to three hours. The time-course of this prolonged enhancement of presynaptic terminal excitability resembled that of long-term potentiation (LTP) which, in contrast, occurs in the post-synaptic sites of hippocampal afferents and some limbic forebrain pathways (Bliss and Lomo,1973; Douglas and Goddard,1975; Racine and Milgram, 1983a, 1983b). It is likely that the prolonged presynaptic changes of the hippocampal output neurones observed in this study reflect changes in the 'plasticity' of the synaptic terminals of HIPP-ACC neurones and thus altered transmission patterns of this pathway.

The prolonged excitability changes following dopamine receptor activation may be associated with the occurrence of some intracellular metabolic events such as the generation of intracellular messenger(s) which mediate a slow phosphorylation-dephosphorylation cycle of membrane ion channel proteins to gate ion fluxes, and consequently, a change in the neuronal excitability (Greengard,1978; Hartzel,1981; Ng and Matus,1979; Williams and Rodnight, 1981). However, activation of striatal D-2 receptors inhibits adenylate cyclase (Onali et al.,1985; Weiss et al.,1985), the enzyme that calayzes the formation of the second messenger, cyclic adenosine monophosphate (cAMP). Nonetheless, other second messengers such as the receptor-activated hydrolysed products of membrane phospholipids: diacylglycerol and inositol triphosphate have been suggested to be associated with neurotransmitter receptors not positively linked to adenyl cyclase (Berridge and Irvine, 1984; Onali et al.,1985). Although there is still a lack of direct evidence, it is possible that D-2 receptor activation triggers a sequence of intracellular metabolic events involving the phospholipid messengers, leading to changes in calcium mobilization (De Vries and Beart,1985) and ion channel protein phosphorylation which may contribute partly to a prolonged alteration of the gating properties of the ion channel(s) (Bernardi et al.,1985; Onali et al.,1982).

Dopamine has been shown to depolarize, ranging up to 20 mV, post-synaptic membranes in mammalian striatal and frontal cortical neurones, primary afferents, and spinal motoneurones (Bernardi et al.,1978; 1982; Gallagher et al.,1980; Herrling and Hull, 1980; Kitai et al.,1976; Krnjevic et al.,1978; Mercuri et al.,1985; Yim and Mogenson, 1986). This depolarization is often associated with a general decrease in membrane conductance, and a clear suppression of spontaneous spike discharge. In hippocampal pyramidal neurones, however, dopamine hyperpolarizes the post-synaptic membrane (Bernardo and Prince, 1982a; 1982b; Herrling, 1981; Suppes et al.,1985). In addition, stimulation of the autoreceptors located on the terminals of nigrostriatal dopaminergic neurones by dopamine agonists tends to suppress the excitability of these neurones suggesting a hyperpolarizing action of dopamine on its own terminals, regulating dopamine release (Mereu et al.,1985; Tepper et al.,1984). These findings indicate clearly that dopamine has multiple actions at different neuronal sites. The results of the present study suggest that dopamine can, via D-2 receptors, depolarize the synaptic terminals of HIPP-ACC neurones(principally glutamatergic, Walaas and Fonnum,1979a), lowering the threshold of excitation and hence, increasing their excitability.

It is known that moderate depolarization of the axonal terminals and the associated reduction of the amplitude of

subsequent action potentials invading the terminals can reduce the quantal release of transmitter (Kusano et al.,1967; Takeuchi and Takeuchi,1964). This mechanism of presynaptic inhibition (Eccles,1964) could partly account for the attenuating effects of the excitatory responses of accumbens neurones to hippocampal stimulation produced by activation of the mesolimbic dopaminergic system via conditioning VTA stimulation. This action of dopamine may contribute to a 'gating' mechanism (Mogenson,1984; Mogenson et al.,1980; Stevens and Livermore,1978)which operates to 'suppress' hippocampal signals that are relayed via the accumbens to motor effector sites in the subpallidal basal forebrain (Mogenson,1984). In addition, considering the nucleus accumbens as one of the prime target sites responsible for the clinical actions of anti-psychotic drugs which block D-2 receptors (Owen et al.,1978; Seeman, 1980), the findings of this study raise questions about the possible role of the D-2 receptors on limbic afferent terminals in the pathogenesis of psychosis which may be mediated partly through mechanisms occurring in the nucleus accumbens (Cross et al.,1981; Matthysee,1981; Stevens,1973). Consistent with this view is the finding that there was a marked reduction of glutamate in the cerebrospinal fluid of schizophrenic patients (Kim et al.,1980) and chronic administration of amphetamine (which releases dopamine)

sensitized glutamate binding sites in rat striatum (Kashiwabara et al., 1984). These findings suggest that 'over-activation' of dopamine D-2 receptors (particularly those on the cortico-striatal neuronal terminals) may lead to the inhibition of striatal glutamate release and contribute to the psychopathology of schizophrenia.

The conclusions drawn from this series of experiments are that dopamine produced a prolonged ennancement of the terminal excitability of HIPP-ACC neurones via direct activation of its D-2 receptor located on the axonal terminals of these neurones. The enhancement of terminal excitability suggests a depolarizing action of dopamine and this may contribute to the 'gating' mechanism which regulates the quantal release of excitatory transmitter from the HIPP-ACC neurone by presynaptic inhibition.

4. Relay of Hippocampal Signals to the Ventral Pallidal and Subpallidal Areas by Way of the Nucleus Accumbens.

In addition to being the site where hippocampal output signals are modulated by the mesolimbic dopaminergic system, the nucleus accumbens is also strategically located to relay the limbic inputs to pallidal motor effector sites. Hippocampal stimulation activated a large proportion of medial accumbens neurones whose locations, as indicated earlier, corresponded with the terminal sites of the glutamatergic hippocampal-accumbens pathway (Kelley and Domesick, 1982; Swanson and Cowan, 1977; Walaas, 1978).

Thirty percent of these neurones, activated by the hippocampal stimulation, were also activated antidromically by stimulation of VP whereas only 7 % of these accumbens neurones were activated antidromically by stimulation of SP. It thus appears that accumbens output neurones project to both VP and SP (Groenewegen et al.,1984; Haber et al.,1985; Nauta et al.,1978; Williams et al.,1977) and transmit incoming signals from the hippocampus. However, hippocampal inputs have a greater access to the accumbens output neurones monosynaptically projecting to VP than to the SP.

The majority of spontaneously active neurones in the VP and SP were inhibited by stimulation of the ventral subiculum of the hippocampus. The recording sites of these neurones also coincided with VP and SP stimulation sites for antidromic activation of accumbens neurones. Moreover, hippocampal stimulation orthodromically excited accumbens neurones (Lopes da Silva et al, 1984) and iontophoretically applied GDEE, a glutamate antagonist, attenuated some of the excitatory responses. Thus the reduction of the inhibitory responses of VP or SP neurones to hippocampal stimulation following microinjection of GDEE into the accumbens suggests that these responses were mediated by first order hippocampal-accumbens glutamatergic neurones (Defrance and Yoshihara, 1975; Lopes da Silva et al.,1984). In addition, there is evidence that neurones that use gamma-aminobutyric

acid as a transmitter project from the nucleus accumbens to the VP and SP (Nagy et al.,1978; Ribak et al.,1979; Walaas and Fonnum, 1979). As indicated earlier, this is based on the observations that lesions in the accumbens depleted GABA markedly in the ventral pallidum (Walaas and Fonnum, 1979) and that the inhibitory responses of VP neurones to accumbens stimulation were blocked by iontophoretic application of picrotoxin, a GABA antagonist (Jones and Mogenson, 1980a; 1980b). It is likely that the inhibitory responses of VP and SP neurones to hippocampal stimulation were due to glutamatergic hippocampal-accumbens neurones activating GABAergic accumbens efferents to VP and SP. Furthermore, with the same number of microelectrode penetrations into the VP and SP, more spontaneously active neurones were recorded in the SP than in the VP. This finding suggests that VP appears to have more silent neurones and accounts for an under-estimation of inhibitory responses of VP neurones to hippocampal stimulation. On the other hand, it is possible that VP neurones receiving accumbens output signals do not project caudally. Instead, these signals may be conveyed from the VP dorsally to the mediodorsal thalamus (MD) and then relayed to the prefrontal cortex (PFC) (Alexander et al.,1986; Haber et al.,1985; Heimer et al.,1982; Krettek and Price, 1977;Siegel et al.,1977; Vives and Mogenson, 1985; Young et al.,1984). In turn, the accumbens also receives prefrontal cortical

projections (Beckstead, 1979; Philipson and Griffiths, 1985). Thus, a feedback loop is completed with accumbens output signals feeding back to the accumbens via the VP-MD-PFC connections, in addition to the accumbens output reaching descending pathway which may convey limbic signals to the MLR of the brainstem (Mogenson, 1984).

The greater variation in the onset latencies of the inhibitory responses in comparison with the VP neurones, following hippocampal stimulation, suggests that the SP responses were mediated multi-synaptically. Hence the fewer antidromic responses of accumbens neurones to SP stimulation may be due to the presence of inter-neurone(s) in the accumbens or in the SP (Barone et al.,1980; Kita and Oomura, 1982; Wayner et al.,1980), since the presence of inter-neurone(s) prevents the recording of antidromic responses (Hunt and Kuno, 1959).

A small number of short-latency excitatory responses to hippocampal stimulation was also recorded in both VP and SP regions. However, the excitatory responses to hippocampal stimulation were encountered less frequently than reported previuosly in other species (Dreifuss and Murphy, 1968; Murphy et al.,1968; Poletti et al.,1973; Powell and Lehman, 1976). Since the majority of these excitatory responses were not reduced by microinjection of GDEE into the accumbens, it is likely that they were not mediated via the accumbens.

Instead the excitatory VP and SP responses to ventral subicular stimulation may be mediated by the medial corticohypothalamic tract or the post-commissural fornix (Palkovits and Zaborsky, 1979; Swanson, 1976; Swanson and Cowan, 1975). On the other hand activation of a striato-pallidal Substance P pathway (Haber and Nauta, 1984) by the excitatory hippocampal input to the accumbens is another possibility for the excitatory SP response to hippocampal stimulation. Furthermore, an unexpected finding in the present study was that a large number of accumbens neurones, not responding antidromically to VP or SP stimulations, were synaptically activated. Since VP and SP are reciprocally connected to the accumbens, stimulation of VP or SP may activate ascending efferents to the nucleus accumbens (Barone et al.,1980; Saper et al.,1979; Swanson and Cowan, 1976).

In conclusion, hippocampal signals to the accumbens were relayed monosynaptically to four times as many VP neurones than to the SP neurones. Hippocampal output signals also reach the SP region by way of the accumbens since the synaptic activation of GABAergic accumbens efferent to the SP by glutamatergic hippocampal-accumbens neurones, was attenuated by the injection of a glutamate antagonist into the accumbens.

5. Signal Transmission From the Hippocampus to the Mesencephalic Locomotor Region By Way of the Nucleus Accumbens and The Subpallidal Area..

The recent anatomical findings of a pathway linking subpallidal neurones with the brainstem MLR region has prompted much speculation about its possible functions in providing the final route by which limbic signals are conveyed to sites in the MLR which generate rhythmic locomotor movement (Swanson et al.,1984). Subpallidal neurones, recorded in the sublenticular substantia innominata and the lateral hypothalamus (Mogenson et al.,1983; Swanson et al.,1984), were antidromically activated by stimulation of the PPN and the adjacent central gray, indicating that efferent SP neurones project monosynaptically to the PPN. However, over 70 % of these SP output neurones were not spontaneously active. This population of silent neurones may represent a separate group of SP-PPN neurones which differ from those which are characterized by their fast discharge rates of 30 to 50 Hz (Jones and Mogenson, 1980; Mogenson et al.,1983; Yim and Mogenson, 1983). Since most of these fast discharging neurones did not respond antidromically to PPN stimulation they are apparently not SP-output neurones. Nevertheless, a number of spontaneously active SP-PPN neurones, antidromically activated by PPN stimulation, were also inhibited orthodromically by stimulating the ventral subiculum of the hippocampus, the origin of the hippocampal

efferent to the nucleus accumbens (Kelley and Domesick, 1982; Lopes da Silva et al.,1984; Swanson and Cowan, 1977). As mentioned in the last section, since stimulation of the hippocampus synaptically activates GABAergic accumbens output neurones to the SP region (Mogenson et al.,1983; Jones and Mogenson, 1980; Nagy et al.,1978), it appears that the inhibitory responses recorded from the SP-PPN neurones to hippocampal stimulation are due to a synaptic activation of GABAergic accumbens efferents to the SP area. Furthermore, the location of stimulation sites from which antidromic responses were elicited in the subpallidal region coincided with those MLR sites which when stimulated, elicited locomotor movements in cats and rats (García-Rill et al.,1981; Skinner and García-Rill, 1984; Mogenson and Wu, 1986). Thus, output signals from the hippocampus can be relayed via the accumbens to the SP neurones which project to the PPN and the adjacent central gray area, an integral part of the 'mesencephalic locomotor region'.

Signal throughput from the hippocampus to the MLR appears to be regulated at the nucleus accumbens. This nucleus is located strategically at one of the first relays for hippocampal efferents (Kelley and Domesick, 1982; Swanson and Cowan, 1977) as well as for the converging mesolimbic dopaminergic afferents which originate from the VTA (Dahlstrom and Fuxe,1964). Microinjection of a

selective dopamine D-2 agonist into the accumbens produced significantly greater attenuation of the inhibitory responses of SP-PPN neurones to hippocampus stimulation than by D-1 agonist injection into the accumbens. This suggests that the hippocampal signal transmission via the nucleus accumbens to the SP, and SP-output neurones to the PPN, are influenced by a D-2 receptor-mediated dopaminergic 'gating' mechanism which suppresses the throughput of the hippocampal signals in the accumbens. This 'gating' mechanism has been investigated by using a terminal excitability test as described in section 3. It appears that dopamine, via a D-2 receptor mechanism, alter the excitability of the axonal terminals of HIPP-ACC neurones and reduce their excitatory transmission. Hance, the dopaminergic 'gating' mechanism in the accumbens which restricts hippocampal signal transmission to the subpallidal sites may be due to a D-2 receptor mediated presynaptic inhibition of HIPP-ACC neurones.

The injection of D-1 or D-2 agonists into the accumbens produced only small changes in the baseline firing pattern of SP neurones. As both D-1 and D-2 dopamine receptors are present on the striatal neurones (Schwarcz et al.,1978; Theodoreu et al.,1981; White and Wang, 1986), it is not known why the D-1 and D-2 agonists administered separately did not activate these post-synaptic receptors on the accumbens-SP neurones to influence SP neurone firing. This raises the possibility that co-activation of both pos-

synaptic D-1 and D-2 receptors is necessary for neurophysiological changes in the SP neurones. Perhaps an additive effect of D-1 and D-2 agonists is needed for activating the accumbens-SP neurones (see Barone et al.,1986; Gershanik et al, 1983; Robertson and Robertson, 1986).

6. Hippocampal Initiation of Locomotor Activity Modified by Dopaminergic D-2 Mechanisms in the Accumbens.

Behavioural responses mediated by the neural connections investigated in the electrophysiological experiments were studied in unanaesthetized animals in order to investigate further whether hippocampal-initiated signals are gated at the accumbens and then relayed via the SP to the PPN. It is known that hippocampal output signals elicit locomotor responses via the nucleus accumbens since the blockade of the glutamatergic hippocampal efferents to the accumbens reduces the hyperkinetic response initiated by carbachol stimulation of the dentate gyrus of the hippocampus (Mogenson and Nielsen,1984a; 1984b). In the present study, N-methyl-D-aspartate, an excitatory acidic amino acid analogue (Watkins and Evans, 1981), which stimulates aspartate receptors preferentially, was used to activate ventral subicular neurones since these neurones receive ventral CA1 pyramidal cell (glutamate/aspartate) projections (Storm-Mathisen,1977). Forward locomotion and explorational

behaviour associated with the hippocampal activities (O'Keefe and Nadel, 1978) were observed following the unilateral NMDA injections into the ventral subiculum, the origin of the hippocampal output neurones to the accumbens. Whether such hyperkinetic movement was partly due to hippocampal epiletiform seisure activity after the NMDA stimulation is not known since no EEG recordings were made. Nevertheless, at the dose of NMDA used (Ø.5 ug) we did not observed behavioural manifestation of seizure activity.

When LY171555, a dopamine D-2 agonst, was injected into the accumbens, no effect on the baseline locomotor activity was observed but a significant reduction of the hyperkinetic effect induced by NMDA injection into the hippocampus resulted. This suggests that the D-2 agonist may exert an inhibitory influence in the accumbens to inhibit the NMDA-induced locomotor responses. Our previous electrophysiological findings, together with biochemical evidence of others (Mitchell and Doggett, 1978; Schwarcz et al.,1981; Theodorou et al.,1981), have implicated a presynaptic D-2 type dopaminergic 'gating' mechanism in regulating the excitatory hippocampal input to the accumbens.

This 'gating' mechanism of dopamine in the accumbens may have an adaptive function in view of the multiple limbic inputs which the accumbens receives (Nauta and Domesick,1982). For example, attenuation of hippocampal input to the accumbens by the D-2 mechanism may enable the

other limbic input(s)(e.g., from the amygdala) to influence the accumbens output neurones to bring about a different adaptive behaviour according to specific environmental demands. This dopaminergic 'gating' mechanism may be analogous to the 'switching' process proposed by Oades (1985) who suggested that ".... an increase of dopamine activity promotes the likelihood of switching between alternative sources of information. The act of swftching may increase the probability of a new input to a given brain region influencing the output and/ or result in an ongoing input being shut off from influencing the output."

In addition to the D-2 receptors located on presynaptic terminals of the striatal afferents in the accumbens, this type of dopamine receptor is also found on the post-synaptic sites of striatal neurones(Schwarcz et al.,1981; Theodorou et al.,1981). At the dose range injected (1-4ug/0.2ul) it is likely that there was direct activation of these post-synaptic D-2 receptors as well. However, following injection of the D-2 agonist directly into the accumbens (present study), or subcutaneous injection of pergolide, another D-2 agonist (Arnt, 1985), there were no increases in locomotor responses similar to those produced by direct injections of dopamine into the accumbens, (Jones and Mogenson,1980; Kelley et al.,1975; Pijnenberg and van Rossum, 1973). The dosage of dopamine used in these previous studies were 20-30

times greater than those used for the D-2 agonist in the present study. Moreover, as indicated earlier, since dopamine stimulates both post-synaptic D-1 and D-2 receptors, perhaps the reason why we did not see any changes in locomotor activity when only a D-2 agonist was injected was the absence of a co-activation of both D-1 and D-2 receptors. Future studies should, therefore, consider a possibile synergistic action of D-1 and D-2 receptors that elicit a dopamine-mediated locomotor response from the accumbens.

7. Hippocampal Initiated Locomotor Activity Mediated Via The Subpallidal Area and The PPN.

The output neurones of the accumbens which receive hippocampal signals may project to the ventral pallidum (Conrad and Pfaff, 1976; Groenewegen et al.,1984; Heimer et al.,1982; Nauta et al.,1978; William et al.,1977) and the subpallidal region, including the sublenticular portion of substantia innominata and the lateral hypothalamus (Mogenson et al.,1983). A substantial portion of this accumbens-subpallidal pathway is GABAergic (Walaas and Fonnum, 1979b; Nagy et al.,1978) and activation of the excitatory hippocampal-accumbens neurones will thus synaptically activate these GABAergic accumbens output neurones to the subpallidal area. For subpallidal neurones to mediate locomotor responses, several pathways have been proposed but the subpallidal-pedunculopontine nucleus connection provides

the most direct route through which subpallidal signals may activate generators of rhythmic limb movements in the PPN (Skinner and Garcia-Rill, 1984; Mogenson and Wu,1986).

In the unanaesthetized animals, increased subpallidal GABA attenuated the hippocampal-initiated hyperkinetic response. Injection of NMDA into the ventral subiculum of the hippocampus may first activate the glutamatergic hippocampal-accumbens neurones (Walaas, 1978; Walaas and Fonnum, 1979a). Then, in the accumbens, the liberated glutamate can release dopamine from the mesolimbic dopaminergic afferents (Arnt, 1981; Donzanti and Uretsky, 1983; Marien et al.,1983; Roberts and Anderson, 1979), which, in turn, elicits an increase in locomotor responses (Jones et al.,1981; Pijnenberg and Van Rossum, 1973). It has been postulated that this dopamine-mediated hyperkinetic response is produced by a post-synaptic action of dopamine which inhibits the GABAergic accumbens output to the subpallidal area (Mogenson, 1984; Walaas and Fonnum, 1979b)) and thus, elevating the amount of GABA present in the SP also attenuated the hyperkinetic response produced by a direct injection of dopamine into the accumbens (Mogen[illegible] and Ni[illegible]en, 1983; Pycock and Horton, 1976; Pycock et al.[illegible] or by releasing dopamine in the accumbens through activation of the glutamatergic synapse (Arnt, 1981; Donzanti and Uretsky, 1983) e.g., by NMDA injection into

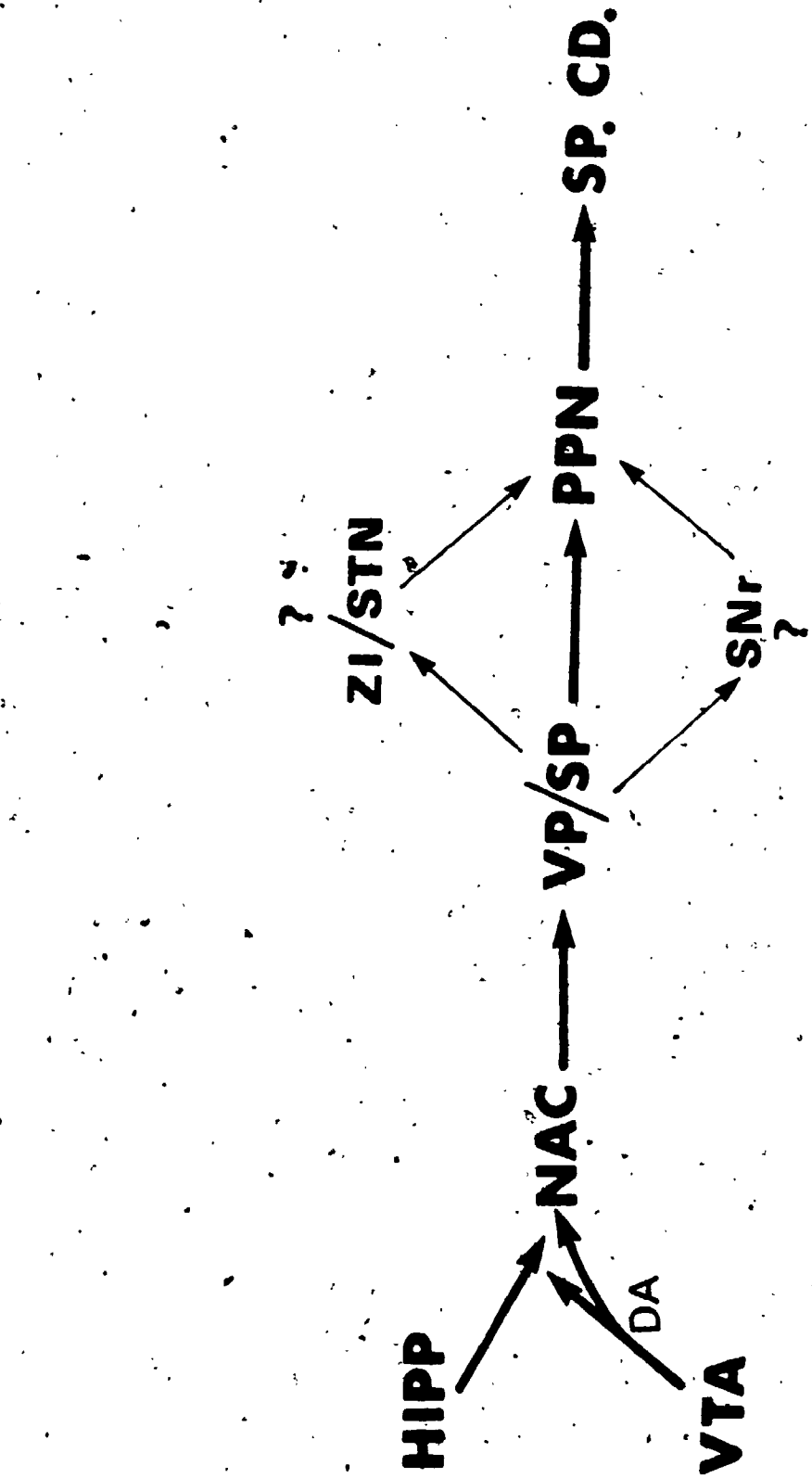
the hippocampus (present study).

The glutamate release in the accumbens from activation of the hippocampal-accumbens pathway may also activate accumbens output neurones to the SP directly and increased locomotor response (Arnt, 1981). If this is the case, then the GABAergic accumbens output neurones would have to inhibit an inhibitory SP-PPN pathway in order to activate the PPN for locomotion. Since stimulation of the SP inhibited 50 % of neurones sampled in the PPN (Swanson et al.,1984), it appears that at least a portion of the SP-PPN pathway is inhibitory. Thus, an alternative intepretation of the NMDA-induced hyperkinetic response was due to a disinhibition of PPN neurones by the accumbens-SP neurones. However, when GABA was elevated pharmacologically (e.g. nipecotic acid injection at 4 ug dose), the NMDA-induced locomotor responses as well as the locomotor response after NPA (4 ug) injection alone into the SP were reduced, rather than potentiated as predicted if GABA in the SP acts by disinhibiting the PPN to elicit locomotor activity. These behavioural observations suggest that the GABAergic accumbens output pathway produces an inhibition of descending SP pathway(s) to suppress hippocampal induced locomotor responses. Although the ventral pallidal and subpallidal outputs descend to the pedunculopontine nucleus and convey signals to the generator site of the MLR for rhythmic limb movements (Mogenson and Wu, 1986; Mogenson et

al.,1985; Haber et al.,1985), other additional outputs also relay subpallidal signals to the PPN, e.g. via the subthalamus(STM, Haber et al.,1985; Hammond et al.,1983; Jackson and Crossman,1981; Rouüzaire-Dubois et al.,1980); zona incerta (ZI; Mogenson et al.,1985; Ricardo,1980;1981; Swanson et al., 1984), or the substantia nigra pars retculata (SNr) (Garcia-Rill et al.,1983; Haber et al.,1985; Hammond et al.,1983; Hopkin and Niessen, 1976). Hence, the reduction of locomotor responses resulting from the pharmacological elevation of GABA in SP may be due to an action of GABA on the SP-SNr-PPN, SP-ZI-PPN or SP-STM-PPN relay cascades (see Fig.36). The net effect of the pharmacological action of GABA that resulted in a reduction of locomotion may be mediated via its inhibitory action on: a) these polysynaptic descending relays from the subpallidal area and masking any possible direct action produced by the SP-PPN pathway, or b) on an excitatory SP-PPN pathway previously demonstrated electrophysiologically (Swanson et al.,1984). In contrast, synaptic activation of accumbens-subpallidal GABAergic pathway(via hippocampal stimulation) may provide a more physiological inhibition of SP output neurones to the PPN, thereby disinhibiting the PPN, and producing an activation of the PPN descending output to the spinal cord to generate locomotor movements.

FIGURE 36.

Schematic of a proposed model illustrating the possible routes by which hippocampal output signals are transmitted to the motor effector sites to elicit locomotor activity. The heavier arrows are the major pathways investigated while the lighter arrows are suggested alternative pathways through hippocampal signals may also reach the PPN, an integral part of the MLR. Abbreviations (from right to left): HIPP, hippocampus; VTA(DA), ventral tegmental area dopaminergic neurones; NAC, nucleus accumbens; VP/SP, vnetral pallidal and subpallidal area; ZI/STN, zona incerta, subthalamic nucleus; SNr, substantia nigra pars reticulata; PPN, pedunculopontine nucleus; SP. CD., spinal cord.


HIPP
NAC
VP/SP
PPN
SP. CD.
VTA
DA
ZI/STN
?
SNr
?

The PPN region, including the adjacent central gray, was shown to mediate hippocampal initiated locomotor responses since procaine injection there reduced significantly the hyperkinetic response from hippocampal stimulation. Nevertheless, procaine did not completely abolish the increase in locomotor responses suggesting that other pathways which by-pass PPN, e.g. the SP-motor cortex projection (McKinney et al.,1983; Saper, 1984), might convey output signals from the hippocampus to spinal sites to increase locomotor responses. This suggestion is further supported by the finding that kainic acid lesion of the PPN decreased, but did not completely abolish, locomotor movement induced by dopamine or amphetamine injection in the nucleus accumbens (Brudzynski and Mogenson,1985).

In summary, the present series of experiments has shown that hippocampal stimulation inhibited spontaneously active SP output neurones to the PPN, a part of the MLR. This inhibitory response was reduced by injecting a selective D-2 agonist into the accumbens. Dopamine exerts a D-2 receptor-mediated 'gating' influence in the accumbens to alter throughput of hippocampal signals to the PPN. In parallel behavioural experiments, NMDA stimulation of hippocampal output neurones produced an increase in locomotor response which was attenuated by D-2 agonist in the accumbens, or by increasing GABA availability in the SP region, or by injecting procaine into the PPN. Combined with results

obtained previously (Mogenson and Nielsen, 1984a; 1984b) it now appears that transmission of hippocampal output signals to the brainstem rhythmic locomotor movement generating sites can be conveyed through the hippocampal-accumbens-subpallidal-pedunculopontine connections.

Finally, as a concluding remark, this pathway may have important adaptive value in view of the known functions of the hippocampus in memory tasks and spatial orientation. Thus, food and water procurement, exploration and location of shelters, or retrieval of pups for maternal care would probably involve the use of the hippocampus to construct a 'cognitive map' which provides the spatial coordinates for these goal-directed movement (O'Keefe and Nadel,1979). Previous studies have suggested an indirect role of the hippocampus in locomotor response initiation. Although hippocampal lesion does not change food or water intake per se (Boitano et al.,1968; 1973; Thomka and Brown, 1975; Murphy et al., 1975), the patterns of motor activity which require spatial information for their executions are disrupted following the hippocampal lesions. These behaviours include hoarding of food back to home cage (Whishart et al.,1970; Wallace and Tigner, 1972) and retrieval of pups by lactating mother rats back to the home cage (Kim , 1960; Kimble et al.,1967; Kubie and Ranck, 1982). According to the environmental demands, initiation

signals for the locomotor components of these behaviours can be inhibited presynatically by a D-2 dopaminergic mechanism (exerted by the VTA mesolimbic dopaminergic afferents) onto the axonal terminals of hippocampal-accumbens neurones. The 'operational advantage' of presynaptic inhibition, particularly in the nucleus accumbens where multiple limbic afferent inputs converge (Phillipson and Griffiths, 1985), is a selective inhibition of one incoming input without inhibiting the accumbens neurone completely by post-synaptic inhibition. Thus, presynaptic inhibition still enables the same accumbens neurone to be activated by other inputs. Furthermore, in view of the post-synaptic action of dopamine in increasing the ratio of the input signals to background discharges in striatal neurones (Wills et al.,1985; Chiodo and Berger,1986), it is conceivable that while this post-synaptic mechanism facilitates the transfer of converging input signals from the one limbic structure, e.g. the amygdala, via the accumbens output neurones to the subpallidal sites, the incoming signals to the accumbens from the other limbic structures, e.g. the hippocampus, are inhibited presynaptically. Accordingly, a more appropriate set of adaptive behaviour mediated by the non-hippocampal limbic input can be expressed by the animal.

SUMMARY

1. Recent neuroanatomical findings have revealed that the nucleus accumbens receives glutamatergic afferents from the ventral subiculum of the hippocampus. The accumbens also receives dense converging dopaminergic neurones from the VTA. The first objective of this study was to use electrophysiological recording techniques to investigate the hippocampal input to the nucleus accumbens and to investigate the possible interaction of the two converging inputs in the accumbens by delivering trains of conditioning pulses to the VTA prior to single-pulse stimulation of the hippocampus. The effects of iontophoretically applied dopamine on the hippocampal-evoked accumbens activity were also compared with that produced by VTA stimulation.

2. Extracellular single unit recordings were made from 109 silent and 77 spontaneously active neurones (mean firing rate of 3-6 Hz) in the medial accumbens of urethane-anaethetized rats. All of these neurones were identified by their excitatory response to stimulation of the ventral subiculum of the hippocampus. The mean onset latency of the excitatory response was 11 ms in the case of the silent neurones and 14 ms in the case of the spontaneously active accumbens neurones.

3. Electrical stimulation of the VTA by conditioning pulses (10Hz) 100ms prior to single-pulse stimulation of the hippocampus attenuated the excitatory response of 41 of 46 (89%) silent accumbens neurones to hippocampal stimulation. The excitatory response of 26 of 30 (87%) spontaneously active neurones to hippocampal stimulation were also attenuated by the VTA stimulation.

4. Iontophoretic application of dopamine (5-30nA) mimicked the attenuating effect on the excitatory responses of 40 (89%) of 45 accumbens neurones to hippocampal stimulation. In 9 out of 10 neurones studied conditioning VTA stimulation first attenuated the excitatory responses of the accumbens neurones. Upon recovery to their control excitatory response, iontophoretic application of dopamine also attenuated the excitatory response of the same accumbens neurones.

5. Destruction of the mesolimbic dopaminergic neurones by 6-hydroxydopamine pretreatment of the VTA 2 days or 7-9 days prior to a recording session abolished the attenuating effect produced by conditioning VTA stimulation in 19 of 25 (76%) silent, and 17 of 18 (94%) spontaneously active neurones. Moreover, the excitatory response of 8 accumbens neurones previously unaffected by stimulation of the VTA in rats which were pretreated with 6-hydroxydopamine, were all attenuated by the iontophoretic application of dopamine.

6. Intraperitoneal injection of haloperidol blocked the attenuating effect on the excitatory response by conditioning VTA stimulation in a total of 36 out of 59 (61%) accumbens neurones studied. In 8 out of 10 neurones studied, iontophoretic application of trifluorperazine, a dopoamine antagonist, blocked the attenuation (by 55-97%) of the excitatory response by conditioning VTA stimulation.

7. Conditioning VTA stimulation or iontophoretic application of dopamine reduced the baseline firing of the accumbens neurones by only 10-15 % whereas the excitatory responses to hippocampal stimulation were markedly attenuated by 40-60 %. This suggests a presynaptic dopamine action which selectively influence the excitatory transmitter release from the hippocampal-accumbens axonal terminals.

8. Since dopamine might have exerted its influence on the excitatory transmission of hippocampal-accumbens neurones presynaptically, the second objective was to use a terminal excitability test to investigate the receptor mechanism by which dopamine alter the excitability of the axonal terminals of these neurones to produce presynaptic inhibition.

9. A terminal excitability test was used to study the effects of dopamine and its selective receptor agonists and antagonists on the electrophysiological properties of

hippocampal-accumbens terminals. Antidromic responses from 283 ventral subicular neurones of the hippocampus were evoked by stimulation of the medial accumbens and the onset latency of 80 % of them were within the range of 10-12 ms. This onset latency range corresponded to the onset latencies of the orthodromic excitatory responses recorded in the accumbens.

10. Baseline firing index of 78 of 110 (71%) hippocampal-accumbens neurones, established by subthreshold accumbens stimulation, was enhanced abruptly by conditioning stimulation of the VTA. The enhancement of the firing index continued for minutes and was of greater magnitude and of longer duration with higher intensity of VTA stimulation.

11. Iontophoretic application of dopamine (60-160 nA, for 30-90 s) onto the axonal terminals of 36 of 70 (51%) hippocampal-accumbens neurones also produced a prolonged enhancement of the firing index similar to that produced by VTA stimulation.

12. Iontophoretic application of sulpiride, a dopamine D-2 antagonist (20-80nA to 9 of 11 neurones), or by intraperitoneal injection (for 5 of 7 neurones) blocked the enhanced firing index of the same neuronal terminals by conditioning VTA stimulation or iontophoretic application of dopamine. No change in the enhanced firing index was

produced by conditioning VTA stimulation in any of the 7 neurones tested when SCH23390, a selective D-1 antagonist, was injected intraperitoneally.

13. The iontophoretic application of the selective D-2 agonist, LY171555, enhanced the firing index in 17 of 31 (55%) hippocampal-accumbens neurones, similar to that produced by dopamine. However, iontophoretic application of SKF38393, a D-1 agonist, produced little change in the firing index over the iontophoretic current range of 40-120 nA. Differential changes of the firing index in response to SKF38393 (no change) and LY171555 (enhanced) was observed in 21 of 35 neurones (60%) tested.

14. The destruction of accumbens neurones by the axon-sparing neurotoxin, ibotenic acid, eliminated the possibility that the effect of the enhanced firing index by dopamine or its D-2 agonist might be mediated indirectly via interneurones or on accumbens-hippocampal feedback pathway. After the lesion, conditioning VTA stimulation still produced an enhanced firing index in 36 of 54 neurones (67%) tested. Furthermore, iontophoretic application of dopamine (10 of 17 neurones) or LY171555 (9 of 15 neurones) also enhanced the firing index of the hippocampal-accumbens in these lesioned rats.

15. In addition to being a site of dopaminergic modulation of limbic input, the nucleus accumbens may provide a functional linkage in relaying hippocampal signals to the motor effector sites in the ventral pallidal and the subpallidal areas which, in turn, are connected to the pedunculopontine nucleus, an integral part of the MLR. The third objective of this study was to determine whether the same accumbens output neurones which received hippocampal input were also activated antidromically by stimulation of the ventral or subpallidal regions. In view of the dopaminergic 'gating' mechanism operating in the accumbens to regulate hippocampal signal throughput, the effects of administration of selective dopamine receptor agonists into the accumbens to alter signal transmission through the accumbens to the MLR-directed subpallidal neurones was also studied.

16. Of the 185 accumbens neurones which were excited by hippocampal stimulation, 55 (30%) of these neurones also responded antidromically to single-pulse stimulation of the ventral pallidum. The mean onset latency of the antidromic responses was 7 ms (range: 4-10ms). In contrast, only (7%) of the accumbens neurones, excited by hippocampal stimulation , were activated antidromically by stimulation of the sublenticular subpallidal area. The mean onset latency of the antidromic responses from these neurones were 8.3 ms (range: 6-9 ms).

17. Recordings were also made in the ventral and subpallidal area in an attempt to find out whether hippocampal signals reached these two pallidal sites. A total of 31 ventral pallidal and 75 subpallidal spontaneously discharging neurones were recorded. The mean firing rate of these neurones was 21 spikes/s (range: 10-35 spikes/s). Hippocampal stimulation inhibited 21 (75%) ventral pallidal neurones and 55 (82%) subpallidal neurones. The mean onset latency of the inhibitory response was 16.3 ms for the ventral pallidal neurones and 17 ms for the subpallidal neurones. 7(18%) ventral pallidal and 12 (2%) subpallidal neurones were excited by hippocampal stimulation.

18. Microinjection of glutamic acid diethyl ester, a glutamate antagonist, attenuated the inhibitory responses of 12 of 17 (75%) ventral pallidal and 9 of 16 (36%) subpallidal neurones to hippocampal stimulation. This suggests that the glutamatergic hippocampal-accumbens neurones relayed their signals via the accumbens by activating the inhibitory accumbens output pathway to the ventral pallidal and subpallidal areas.

19. Sixty one(33%) of the 185 accumbens neurones synaptically activated by hippocampal stimulation were also activated synaptically by the stimulation of ventral pallidum (mean onset latency=6.2ms) and 8 (7%) were

synaptically activated by subpallidal stimulation (mean onset latency=7.5ms).

20. Further studies were made to determine whether the subpallidal neurones which receive hippocampal signals project to pedunculopontine nucleus, an integral part of the MLR. 236 Subpallidal neurones were recorded in the sublenticular subpallidal region. Of these neurones 156 (66%) were antidromically activated by stimulation of the medial pedunculopontine nucleus and the adjacent lateral portion of the central gray. The spontaneous activity of 30 (19%) of these subpallidal neurones was inhibited by hippocampal stimulation. On the other hand, 75% (118 of 156 neurones) of these subpallidal neurones were silent and had a longer mean antidromic onset latency of 13 ms, when compared to the spontaneously active subpallidal neurones which have a mean antidromic onset latency of 6 ms. It appears that the silent and spontaneously active pedunculopontine-directed subpallidal neurones belong to different populations of neurones.

21. Microinjection of LY171555, but not SKF38393, into the accumbens attenuated the inhibitory responses of the same eight subpallidal neurones to hippocampal stimulation. Since these same subpallidal neurones also responded antidromically to pedunculopontine stimulation, it appears

that D-2 receptor in the accumbens regulated the hippocampal output signal throughput to the pedunculopontine nucleus via the subpallidal area.

22. In two separate groups of 10 subpallidal neurones not activated antidromically pedunculopontine stimulation, microinjection of the D-2 agonist, attenuated the inhibitory responses to hippocampal stimulation significantly more than the attenuation produced by D-1 agonist.

23. The baseline firing rate of subpallidal neurones were generally not influenced by the separate injection of the dopamine D-1 and D-2 agonists into the accumbens. However, baseline firing of 2 subpallidal neurones increased by 20-30 % following injection of the D-2 agonist into the accumbens, while the injection of the D-1 agonist into the accumbens had a tendency to reduce the overall firing rate of 2 subpallidal neurones by 10-20 %.

24. To further investigate the dopamine D-2 receptor regulation of the hippocampal-initiated locomotor activity in freely-moving rat, the fourth objective of this study was to elicit the locomotor activity by chemical activation of the hippocampus. The effects of dopamine agonist injected into the accumbens on this elicited response was studied. The hippocampal-elicited motor activity was also studied

when neuronal blockers were microinjected into the subpallidal area and the MLR region in an attempt to study whether the hippocampal signals transmitted via this connection mediated the locomotor response.

25. Unilateral injection of N-methyl-D-aspartate acid, an excitatory amino acid were made into the ventral subiculum of 21 freely moving rats. The spontaneous locomotor activity of these rats was increased 3-4 fold when compared with the saline injection.

26. The NMDA-induced hyperkinetic responses was reduced in a dose-dependent manner by injection of the D-2 agonist into the accumbens (n=7 rats, 14 injection sites). Similar reduction of the NMDA-induced hyperkinetic responses were also observed following microinjection of nipecotic acid or procaine into the subpallidal area (n=9 rats, 18 injection sites), or procaine into the pedunculopontine nucleus (n=6 rats, 12 injection sites).

27. In conclusion, results from these experiments have indicated that the nucleus accumbens receives prominent excitatory input from the ventral subiculum of the hippocampus. Dopamine released from the converging mesolimbic dopaminergic neurones of the VTA attenuated the excitatory throughput of the hippocampal output signals by raising the excitability of the axonal terminals of

hippocampal-accumbens neurones via a D-2 receptor-mediated mechanism, to produce presynaptic inhibition of this excitatory transmission. In addition from being the site of the dopaminergic 'gating' mechanism, the nucleus accumbens also provides a linkage between the hippocampus and the ventral and subpallidal areas by relaying hippocampal output signals to these two pallidal motor effector sites. In turn, the subpallidal output to the MLR may provide a common pathway through which hippocampal signals are transmitted via the accumbens and the subpallidal area and subsequently activates the brainstem MLR sites to generate rhythmic locomotor movements.

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